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ERRATA.

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Page	Line	
78	31	*for* "$C_{13}H_{22}O_4$" *read* "$C_{22}H_{22}O_4$."
534	17	*for* "dinitration" *read* "mononitration."
602		In formula (II), the arrow should mark the bond between CO and O.

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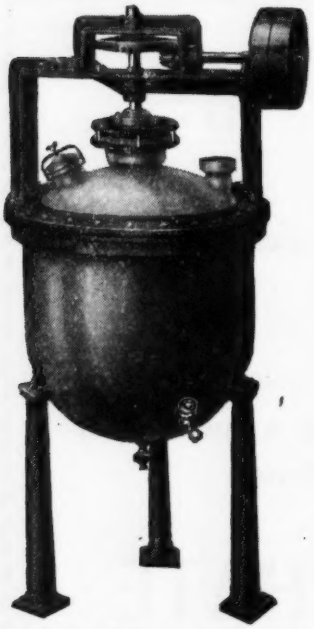

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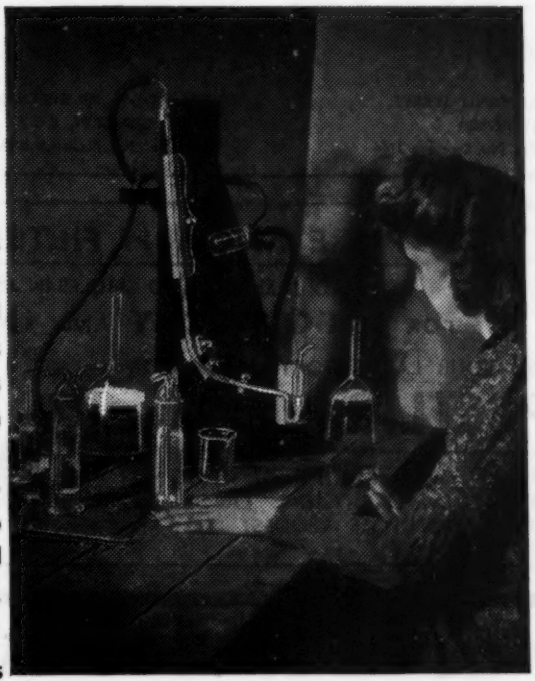

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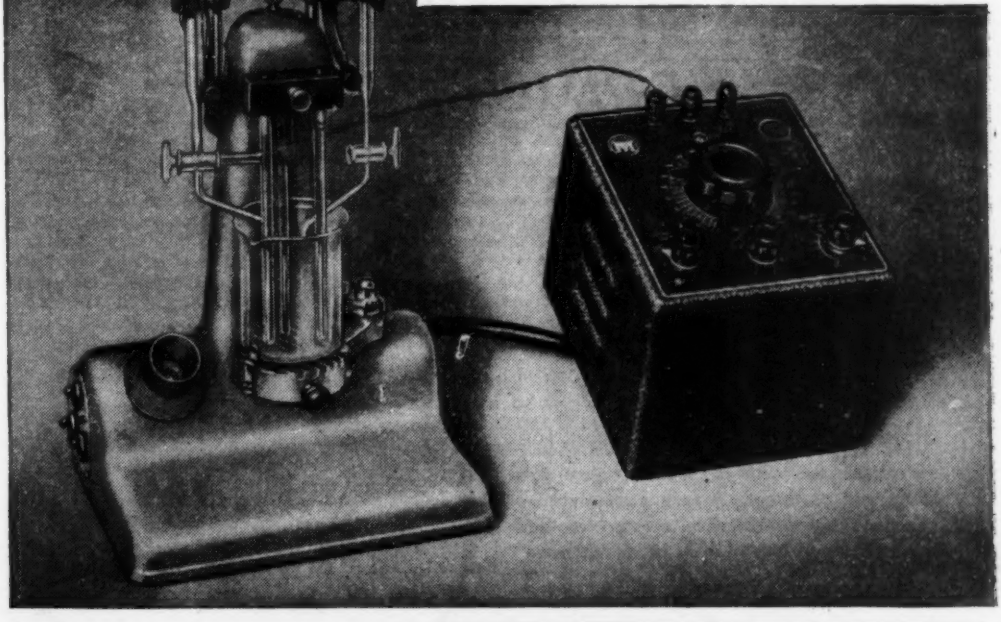

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during the first 5 minutes with considerable frothing; the mixture was subsequently stirred for 24 hours. The 3 : 3′-*dichloro*-4 : 4′-*dinitrodiphenyl* formed (2·1 g.) was isolated as above; it crystallised three times from boiling glacial acetic acid as cream micro-needles, m. p. 226—230° (Found: N, 7·1. $C_{12}H_6O_4N_2Cl_2$ requires N, 6·9%).

The authors are indebted to the Charles Brotherton Trust for a Research Scholarship to one of them (E. R. W.), and to Imperial Chemical Industries Ltd. (Dyestuffs Division) for gifts of chemicals.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, June 6th*, 1946.]

NOTES.

1 : 2 : 3 : 4-*Tetrahydroisoquinaldinic Acid*. By W. SOLOMON.

iso*Quinaldinic Acid*.—1-Cyano-2-benzoyl-1 : 2-dihydro*iso*quinoline, obtained from *iso*quinoline, benzoyl chloride, and aqueous potassium cyanide (Reissert, *Ber.*, 1905, **38**, 3427), is best hydrolysed to *iso*-quinaldinic acid by boiling with 10 vols. of 65% sulphuric acid for 2 hours (cf. Padbury and Lindwall, *J. Amer. Chem. Soc.*, 1945, **67**, 1269). The crude yield in the form of copper salt is 83%. The free acid is best crystallised from 7—8 parts of hot water. The yield of the acid so purified, calculated on the original cyano-compound, is 58%; m. p. 168—171° (froths).

1 : 2 : 3 : 4-*Tetrahydroisoquinaldinic Acid*.—*iso*Quinaldinic acid (24 g.) in glacial acetic acid (288 c.c.) at atmospheric pressure and *ca.* 50°, absorbed, in the presence of Adams's platinum oxide catalyst (1·6 g.), the calculated volume of hydrogen (6·5 l. at N.T.P.) in 13 days' intermittent shaking. The catalyst had to be highly active to effect even this rate of absorption. After filtration and removal of solvent under reduced pressure, the residue was triturated with alcohol and the resulting solid collected and washed with alcohol. Only 15·9 g. were obtained, the filtrate containing a further 10·5 g. of uncrystallisable material whose nature at present remains unknown. The solid, on crystallisation from a boiling mixture of alcohol (10 vols.) and water (20 vols.), furnished the *tetrahydro-acid* in colourless plates, m. p. 299° (decomp.) after softening (Found: C, 67·7; H, 6·3; N, 7·55. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3; N, 7·9%). The N-*benzoyl* derivative, obtained by the method of Steiger (*J. Org. Chem.*, 1944, **9**, 396), separated from alcohol in hard, dazzlingly white incrustations of colourless plates, m. p. 120° (decomp.) after sintering at 110° (Found: C, 72·4; H, 5·6; N, 4·9. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·4; N, 5·0%). This derivative, on esterification with methanol and sulphuric acid, furnished *methyl* N-*benzoyl*-1 : 2 : 3 : 4-*tetrahydroisoquinaldinate*, large transparent prisms, m. p. 105—108°, from methanol, sparingly soluble in ether, but readily in other solvents (Found: C, 73·4; H, 5·8; N, 4·8. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8; N, 4·7%).

The author's thanks are due to Messrs. A. W. Stokes and H. Waddington for experimental assistance and to Mr. A. Bennett for the micro-analyses.—WELLCOME LABORATORIES OF TROPICAL MEDICINE, LONDON, N.W.1. [*Received, April 18th*, 1946.]

***Diglycylethylenediamine*.** By T. L. COTTRELL and J. E. GILL.

PFEIFFER and SAURE (*J. pr. Chem.*, 1941, **157**, 116) obtained, by ammonolysis of bischloroacetylethylene-diamine under fairly drastic conditions, a compound which they considered to be diglycylethylene-diamine. They reported a viscous oil, which on long standing gave hygroscopic crystals. No m. p. or analytical figures were given, and it was characterised as the picrate, m. p. 238—241°.

We have obtained diglycylethylenediamine as a crystalline, non-hygroscopic material in good yield. The difference between our method of preparation and that of Pfeiffer and Saure was in the use of milder conditions of ammonolysis (cf. Cheronis and Spitzmueller, *J. Org. Chem.*, 1941, **6**, 349), and in the method of isolation of the base from the hydrochloride. For this they used silver oxide, but we noted that the base tended to form a soluble silver complex.

The compound was strongly basic; its behaviour with copper hydroxide was similar to that of the compound described by Pfeiffer and Saure.

Experimental.—Bischloroacetylethylenediamine. Bergell's method (*Z. physiol. Chem.*, 1922, **123**, 280) for the preparation of this compound gave only a 14% yield, so the following method was adopted. 22·7 G. of chloroacetyl chloride, dissolved in 60 ml. of dry chloroform, were added slowly with cooling and stirring to 14·7 g. of ethylenediamine in 100 ml. of dry chloroform. The solid was filtered off and extracted with hot absolute alcohol to give 15·2 g. of crude bischloroacetylethylenediamine. This was recrystallised from absolute alcohol, giving 12·5 g. (59%) of pure compound, m. p. 175° (Bergell gives m. p. 171—172°). The compound could also be prepared from chloroacetic ester and ethylenediamine.

Diglycylethylenediamine. A mixture of 14·1 g. of the foregoing compound, 105 g. of ammonium carbonate in 90 ml. of water, and 120 ml. of ammonia (*d* 0·88) was kept at room temperature for 18 hours, heated to 55° for 4 hours, and then filtered. The clear filtrate was evaporated to dryness under reduced pressure and extracted with 300 ml. of absolute alcohol under reflux. The residue was dissolved in the minimum quantity of water, and poured into 200 ml. of absolute alcohol. The precipitate, which consisted of the crude hydrochloride, was filtered off (11·7 g., 70%). Recrystallised from aqueous alcohol, it had m. p. 246° (decomp.).

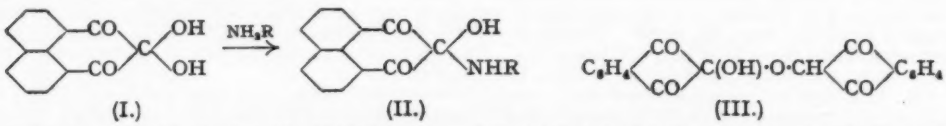
7 G. of the hydrochloride were converted into the base by adding 57 ml. of N-sodium hydroxide solution, evaporating to dryness, and extracting the residue with butanol. The base, crystallised from butanol, had m. p. 157—158° (yield theoretical) (Found: C, 41·3; H, 8·03; N, 31·4. Calc. for

$C_8H_{14}O_2N_4$: C, 41·3; H, 8·05; N, 32·2%) and formed non-hygroscopic needles. The picrate had m. p. 240° (decomp.). The acetyl derivative, recrystallised from aqueous alcohol or water, had m. p. 278—279° (Found: Ac, 32·6. Calc. for $C_{10}H_{18}O_4N_2$: Ac, 33·3%).

Attempts to prepare diglycylethylenediamine by condensation of ethylenediamine with glycyl chloride or glycine were unsuccessful. From glycine ester a very small yield of the substance was obtained.—IMPERIAL CHEMICAL INDUSTRIES LIMITED, EXPLOSIVES DIVISION, RESEARCH DEPARTMENT, STEVENSTON, AYRSHIRE. [*Received, April 25th*, 1946.]

Derivatives of peri*Naphthindanetrione.* By RADWAN MOUBASHER and (MRS.) AKILA MOSTAFA.

ERRERA and SORGES (*Gazzetta*, 1913, **43**, ii, 625) stated that aniline reacts with *peri*naphthindane-1 : 2 : 3-trione hydrate to form a substance believed to be (II, R = Ph), but they did not describe the substance apart from stating that it decomposes on heating. We obtained this compound in intense yellow crystals and also the p-*chloroaniline* analogue. With benzidine a *substance* was obtained formed by condensation of equimolecular amounts. Alkaline hydrolysis in the presence of air produced naphthalic acid and aniline, *p*-chloroaniline, or benzidine, respectively. Acid hydrolysis afforded the bases together with the trione hydrate.



(I.) (II.) (III.)

Schönberg and Moubasher (*J.*, 1944, 366) showed that triketohydrindene is photochemically reduced in sunlight by *iso*propyl alcohol to the colourless product (III; see Ruhemann, *J.*, 1911, **99**, 797), and we find that *peri*naphthindanetrione behaves similarly, giving a colourless product (isolated as a *dihydrate*) believed to be of analogous structure, although a symmetrical constitution, >C(OH)·C(OH)<, is not excluded.

Action of peri*Naphthindane*-1 : 2 : 3-*trione Hydrate on Bases.*—(*a*) *Aniline.* The hydrate (1 g.), dissolved in water at room temperature, was treated dropwise with aniline (6 g.). Yellow needles were formed almost at once, and after standing for a short time the 2-anilino-2-hydroxy*peri*naphthindane-1 : 3-dione (II, R = Ph) was filtered off and crystallised from 50% alcohol; m. p. about 230° (decomp.), depending on the rate of heating; yield, 1·3 g. (Found: C, 75·6; H, 4·4; N, 4·7. Calc. for $C_{19}H_{13}O_3N$: C, 75·2; H, 4·3; N, 4·6%).

(*b*) p-*Chloroaniline.* The 2-p-*chloroanilino*-analogue, similarly prepared, formed yellow crystals, m. p. 220°; yield, 1·5 g. (Found: C, 66·9; H, 3·5; N, 3·9; Cl, 10·5. $C_{19}H_{12}O_3NCl$ requires C, 67·5; H, 3·6; N, 4·1; Cl, 10·5%).

(*c*) *Benzidine.* The reaction was carried out in a mixture of equal volumes of water and alcohol, containing *peri*naphthindane-1 : 2 : 3-trione (1 g.) and benzidine (0·82 g.). 2-*Benzidino*-2-*hydroxy*peri-*naphthindane*-1 : 3-*dione* (II, R = $C_6H_4{\cdot}C_6H_4{\cdot}NH_2$) was crystallised from ethyl alcohol; m. p. 270° (decomp.); yield, 1·4 g. (Found: C, 75·6; H, 4·6; N, 7·0. $C_{25}H_{18}O_3N_2$ requires C, 76·1; H, 4·6; N, 7·1%).

The first two compounds were soluble in benzene and alcohol, and the last in the hot solvents. The colours given in concentrated sulphuric acid were, respectively, an intense violet, green, and red.

Hydrolysis of Condensation Products.—(*a*) *In acid solution.* 1 G. of the substance was refluxed with a mixture of 25 c.c. of hydrochloric acid (*d* 1·1) and 25 c.c. of water for 15 minutes. On cooling, colourless crystals of the trione hydrate were obtained, which after crystallisation had m. p. and mixed m. p. 273°. The solution contained aniline, *p*-chloroaniline, or benzidine.

(*b*) *In alkaline solution.* 1 G. of the substance was refluxed for 15 minutes with aqueous sodium hydroxide solution (10%; 50 c.c.), and the blue solution was cooled and decolorised by shaking with air. The mixture was extracted with ether, and the extract, on evaporation, yielded aniline, *p*-chloroaniline, or benzidine. The aqueous solution in each case on acidification yielded naphthalic acid (m. p. and mixed m. p. 274° after crystallisation from benzene).

Photo-reduction of peri*Naphthindane*-1 : 2 : 3-*trione with* iso*Propyl Alcohol.*—The trione (2 g.) was suspended in freshly distilled *iso*propyl alcohol (10 c.c.) in a sealed "Pyrex" tube, in an atmosphere of carbon dioxide. The tube was exposed to sunlight for a week (in April). The resulting yellow solid was filtered off, and the excess of alcohol evaporated in a vacuum. The solid mass recrystallised from benzene to form pale yellow needles of a *dihydrate* (1·1 g.), m. p. 220° (decomp.), soluble in alcohol and acetic acid (Found: C, 67·6; H, 3·9. $C_{16}H_{14}O_6.2H_2O$ requires C, 68·1; H, 3·9%).

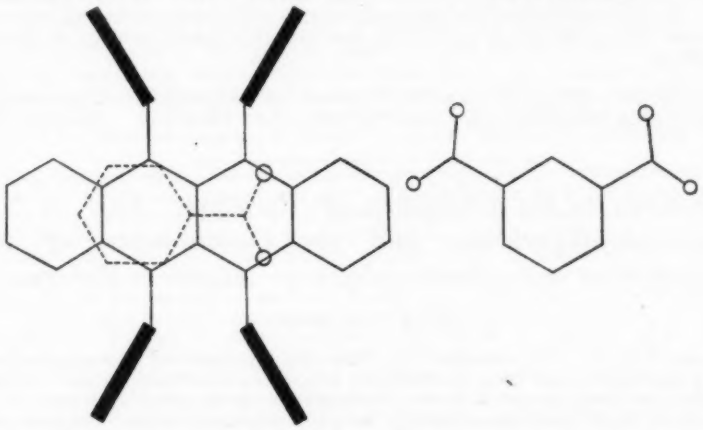
The photo-product (0·5 g.) was refluxed with 25 c.c. of sodium hydroxide solution (20%) for 15 minutes. The blue solution was cooled, and shaken with air until decolorised; from this solution naphthalic acid (identified as above) was obtained. The same acid (m. p. and mixed m. p. 274°) was isolated as a colourless sublimate when the photo-product was heated with selenium in a stream of oxygen at 220° (bath temp.).—FOUAD I UNIVERSITY, CAIRO, EGYPT. [*Received, April 26th*, 1946.]

Stereo-effects and van der Waals Complexes. By E. J. BOWEN and E. COATES.

The quenching of the fluorescence of aromatic hydrocarbons in solution by other aromatic molecules is often due to the formation of comparatively stable van der Waals complexes (Bowen, Barnes, and Holliday, *Trans. Faraday Soc.*, 1946, to appear), and in other cases, where the life of the complex is very short, to collisions governed by diffusion. We find that the quenching of the fluorescence of rubrene

in hexane solution by nitrobenzene arises from complex formation with a heat of formation of 2·5 k.-cals./mole, and *m*-dinitro- and *s*-trinitro-benzene behave as collisional quenchers. The reason for this difference in behaviour, which is the opposite of that which would be expected at first sight from the work of Briegleb (*Z. physikal. Chem.*, 1932, *B*, **19**, 255; 1934, *B*, **26**, 63; 1935, *B*, **27**, 474; 1935, *B*, **31**, 58; 1936, *B*, **32**, 305) on the stability of hydrocarbon–nitro-compound complexes, is apparent from the figure. The nitrobenzene molecule can accommodate itself parallel to the naphthacene centre of

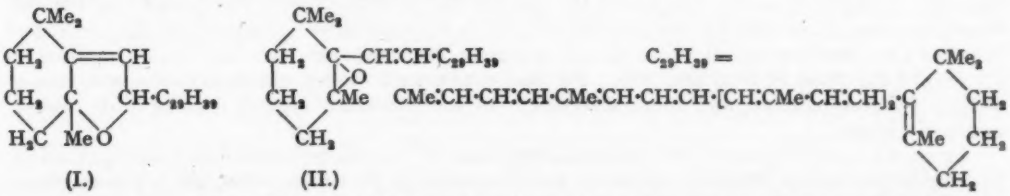
Rubrene and Nitrobenzene. m-*Dinitrobenzene.*



the rubrene molecule, but the polynitro-compounds cannot because of interference from the four phenyl groups which are not coplanar with the centre. This affords further evidence of the structure of hydrocarbon–nitro-compound complexes as parallel molecular orientations.—PHYSICAL CHEMISTRY LABORATORY, SOUTH PARKS ROAD, OXFORD. [*Received, May 22nd*, 1946.]

The Pro-vitamin-A Activity of Mutatochrome. By N. T. GRIDGEMAN, R. F. HUNTER, and N. E. WILLIAMS.

MUTATOCHROME (I) (Karrer and Jucker, *Helv. Chim. Acta*, 1945, **28**, 27), which Euler, Karrer, and Walker (*ibid.*, 1932, **15**, 1507) originally supposed to be β-carotene epoxide ("β-carotene oxide") (II), shows growth-promoting activity in rats not closely similar to that of β-carotene as stated by the original authors but appreciably less than that of α-carotene.



This result and the 1 : 2 ratio for biological activity of α- to β-carotene (Kuhn and Brockmann, *Klin. Wochenschr.*, 1933, **12**, 972; Kuhn, Brockmann, Scheunert, and Schieblich, *Z. physiol. Chem.*, 1933, **221**, 129; Wilkinson, *Biochem. J.*, 1941, **35**, 824) are consistent with the view that the conversion of β-carotene into vitamin-A which occurs *in vivo* involves the fission of the central double bond in the former (cf. Hunter, *Chem. and Ind.*, 1942, **61**, 89). Similar but less precise evidence on the same point is furnished by the earlier observations of Kuhn and Brockmann (*Ber.*, 1933, **66**, 1319) and Kuhn and Grundmann (*Ber.*, 1934, **67**, 593) that semi-β-carotenone and cryptoxanthin show growth-promoting activity in daily doses of 5—10 μg. in contrast to β-carotene which is effective in doses of 2·5 μg.

Experimental.—The following experiment on the preparation of mutatochrome is typical:

A solution of β-carotene (0·55 g.) in chloroform (100 c.c.) was treated with perbenzoic acid in the same solvent (1·2 mols.; 3·2 c.c.) and kept at 0° in an atmosphere of carbon dioxide for 42 hours. The solution was washed with aqueous sodium bicarbonate (5%), dried (Na_2SO_4), and evaporated under reduced hydrogen pressure with the usual precautions (Hunter and Scott, *Biochem. J.*, 1941, **35**, 31) at a temperature below 50°. The mutatochrome, which was separated by chromatography on alumina as a typical lemon-yellow zone, was rechromatographed and crystallised from acetone, from which it separated in small yellow-brown crystals, m. p. 158°, which showed absorption maxima at 487 and 456mμ in carbon disulphide and at 464 and 437mμ in chloroform ($E^{1\%}_{1\,cm.}$ = 1910 and 2190, respectively, for latter solvent). It showed a transient band at 5950 A. in the antimony trichloride reaction.

The yield of mutatochrome varied from 5 to 12% but attempts to increase this by variation of concentration of perbenzoic acid, temperature, and time proved unsuccessful (cf. Euler, Karrer, and Walker, *loc. cit.*).

Biological assay. Mutatochrome was dissolved in refined deodorised arachis oil containing 0·01% of quinol and the pro-vitamin-A activity of the solution in Wistar rats was compared with that of the International Standard preparation (1934) of β-carotene diluted with arachis oil. A total of 87 vitamin-A deficient rats, in 27 isogenic sets (11 tetrads, 11 triads, and 5 pairs), was used in a 4-point experimental design (Gridgeman, *Biochem. J.*, 1943, **37**, 127), with daily doses of (i) 0·54 μg. mutatochrome, (ii) 0·72 μg. β-carotene, (iii) 0·9 μg. mutatochrome, and (iv) 1·2 μg. β-carotene over a 3-week period. As group (i) grew less than group (ii) and group (iii) less than group (iv), it was at once obvious that the mutatochrome was appreciably less than 75% as potent as β-carotene. The actual assay, expressed as weight for weight activity of mutatochrome in terms of β-carotene, was 39%, the ($P = 0·95$) fiducial limits of error being 29 to 47%. As the International Standard preparation of β-carotene is known to be less than 100% pure, mutatochrome has certainly less than 47%, and probably less than 39%, of the pro-vitamin-A activity of β-carotene.

We thank the Directors of Lever Brothers and Unilever Ltd. for permission to publish these results.—RESEARCH DEPT., LEVER BROTHERS AND UNILEVER LTD., PORT SUNLIGHT. [*Received, May 1st,* 1946.]

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34. *Contributions to the Chemistry of Pyridine. Part II. 3- and 5-Hydroxy-2-methylpyridine, and the Condensation of 5-Hydroxy-2-methylpyridine with Formaldehyde in Alkaline Medium.*

By T. URBANSKI.

" β-Hydroxy-α-picoline ", obtained by the sulphonation of 2-methylpyridine and subsequent alkali fusion, has been shown to be 5-hydroxy-2-methylpyridine. 3-Hydroxy-2-methylpyridine has been prepared from 3-hydroxy-2-hydroxymethylpyridine. 5-Hydroxy-2-methylpyridine reacts with formaldehyde to yield 5-hydroxy-2-methyl-6-hydroxymethylpyridine.

" β-HYDROXY-α-PICOLINE " was first prepared by Wulff (G.P. 541,681/1928, F.P. 685,583/1930) by alkali fusion of 2-methylpyridine-3-sulphonic acid (obtained according to G.P. 541,036/1928 and F.P. 685,062/1930 by sulphonation of 2-methylpyridine). Wulff did not establish the structure of his product and suggested the 3- and the 5-position as alternatives for the hydroxyl group. Later, Graf (*J. pr. Chem.*, 1932, **133**, 35) prepared 5-hydroxy-2-methylpyridine from 6-methylnicotinic acid. Finally, Aso (*Bull. Inst. Phys. Chem. Res. Tokyo*, 1939, **18**, 182; *J. Agric. Chem. Soc. Japan*, 1940, **16**, 249) isolated 5-hydroxy-2-methylpyridine from the products of reaction between hexoses or 5-methylfurfuraldehyde and ammonium salts.

All these authors gave practically the same m. p. of the substance, varying from 164° to 167°. Aso also prepared from his compound the picrate, m. p. 202—203°. The present author has found the same m. p. 202° for the picrate of " β-hydroxy-α-picoline " prepared by the method of Wulff. The identity of all these m. ps. suggests that the product by Wulff's method is identical with those of Graf and Aso. No final evidence, however, exists as to the structure of Wulff's hydroxypicoline, and some statements in the literature suggest it to be 3-hydroxy-2-methylpyridine.

From the resinous products of the oxidising fusion of " β-hydroxy-α-picoline " with potassium hydroxide, the known 5-hydroxypicolinic acid (Bellman, *J. pr. Chem.*, 1884, **29**, 7) has now been isolated. This is evidence that Wulff's product is 5-hydroxy-2-methylpyridine.

The same acid has been isolated in a larger quantity from the by-products of the alkali fusion of 2-methylpyridine-3-sulphonic acid. It is evidently formed from 2-methylpyridine-5-sulphonic acid through 5-hydroxy-2-methylpyridine.

A further proof of the structure of this compound has been obtained by preparing *3-hydroxy-2-methylpyridine*, the parent substance of pyridoxine, by reduction of 3-hydroxy-2-bromomethylpyridine (Part I, *J.*, 1946, 1104) by means of zinc dust.

5-Hydroxy-2-methylpyridine reacts with formaldehyde to form *5-hydroxy-2-methyl-6-hydroxymethylpyridine*. To establish the position of the hydroxymethyl group, the substance was oxidised to the corresponding acid. Because of the phenolic character of 3-hydroxy-derivatives of pyridine, it was necessary to methylate the substance before oxidation. The oxidation with potassium permanganate in alkaline medium led to the formation of *3-methoxy-6-methylpicolinic acid* which on demethylation with hydrobromic acid gave *3-hydroxy-6-methylpicolinic acid.*

EXPERIMENTAL.

5-Hydroxypicolinic Acid.—(*a*) " β-Hydroxy-α-picoline " (2 g.) prepared according to Wulff (*loc. cit.*) was fused with potassium hydroxide (5 g.) in a nickel crucible for 2 hours at 240—260°. The melt was

dissolved in water, neutralised with hydrochloric acid, acidified with acetic acid, and filtered, and the 5-hydroxypicolinic acid was precipitated as its cupric salt. This was collected and decomposed with hydrogen sulphide, and the solution of the acid was evaporated to dryness. A few mg. of 5-hydroxypicolinic acid were isolated; crystallised from water it had m. p. 260° (Bellmann, *loc. cit.*, gives 258°).

(*b*) The ammonium salt of 2-methylpyridine-3-sulphonic acid (75 g.) was fused with potassium hydroxide as described by Wulff. The mass was dissolved in water (200 c.c.), neutralised (phenolphthalein) with hydrochloric acid, and acidified (litmus) with acetic acid. 5-Hydroxy-2-methylpyridine was collected. The filtrate was treated with cupric acetate, boiled, and the precipitate of cupric salt collected. The salt was decomposed with hydrogen sulphide, and the filtrate evaporated to dryness. The resinous product crystallised on standing. The crystals were washed with a small amount of cold water, dissolved in hot water, and acidified with acetic acid, and the silver salt was precipitated with silver acetate. It was collected, decomposed with hydrogen sulphide, and the filtrate evaporated. The crystalline solid residue was recrystallised from water (twice) and then had m. p. 263—264°, mixed m. p. with 5-hydroxypicolinic acid prepared as in (*a*), 260°. Yield 0·4 g. (Found: N, 9·1. Calc. for $C_6H_5O_3N,H_2O$: N, 8·9%). A small sample decomposed by heating with calcium oxide gave a distillate of 3-hydroxypyridine; after resublimation this had m. p. 120° alone or in admixture with an authentic specimen.

3-*Hydroxy*-2-*methylpyridine*.—3-Hydroxy-2-hydroxymethylpyridine hydrochloride (2 g.) (Part I, *loc. cit.*) was dissolved in 60% hydrobromic acid (20 c.c.) and boiled under reflux for ½ hour. The resulting solution of 3-hydroxy-2-bromomethylpyridine hydrobromide was cooled below − 10° and zinc dust (8 g.) and 30% hydrobromic acid (30 c.c.) were added in small portions during 2 days, the temperature being kept below − 5°. On the third day the mixture was warmed on a water-bath until all the zinc had dissolved. The solution was cooled, made alkaline with 10% sodium carbonate (phenolphthalein), filtered from the precipitate, neutralised with dilute sulphuric acid, evaporated, and extracted with acetone. The extract was evaporated and extracted with hot ethyl acetate. 3-*Hydroxy*-2-*methylpyridine* crystallised on cooling in white needles. Yield, 0·95 g. (70%). After two sublimations under reduced pressure it had m. p. 160—161° (Found: C, 66·2; H, 6·7; N, 12·7. C_6H_7ON requires C, 66·1; H, 6·4; N, 12·8%). It was soluble in hot water, insoluble in chloroform, carbon tetrachloride, or benzene; more soluble in ether, acetone, or ethyl or amyl acetate than was 5-hydroxy-2-methylpyridine. It gave with ferric chloride a wine-red colour which differed slightly from the reddish-brown colour given by 5-hydroxy-2-methylpyridine. The *picrate* crystallised from water as light yellow needles, m. p. 192° (Found: N, 16·4. $C_{12}H_{10}O_8N_4$ requires N, 16·6%).

5-*Hydroxy*-2-*methyl*-6-*hydroxymethylpyridine*.—5-Hydroxy-2-methylpyridine (5·45 g., 0·05 mol.) was dissolved in 10% aqueous sodium hydroxide (22 c.c.) and 36% formaldehyde solution (13·6 c.c., 0·15 mol.). The solution was refluxed on the water-bath for 1½ hours. After cooling it was acidified with glacial acetic acid (4·5 c.c.) and evaporated. The residue was extracted with acetone (*ca.* 500 c.c.), the acetone distilled off, and the free 5-hydroxy-2-methyl-6-hydroxymethylpyridine crystallised out. After recrystallisation from water (yield, 5·2 g.; *ca.* 75%) and then from alcohol it formed plates, m. p. 154°. It was readily soluble in hot water, alcohol, or acetone, and gave a cherry-red colour with ferric chloride (Found: C, 60·4; H, 6·3; N, 10·1. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1%). The hydrochloride was prepared by rubbing the base in a mortar with hydrochloric acid. After two recrystallisations from aqueous acetone it had m. p. 162° (Found: N, 7·7; Cl, 19·7. $C_7H_9O_2N,HCl$ requires N, 8·0; Cl, 20·3%). The picrate, precipitated from an alcoholic solution and washed with alcohol, had m. p. 173—174° (Found: N, 15·0. $C_{13}H_{12}O_9N_4$ requires N, 15·2%).

5-*Hydroxy*-2-*methyl*-6-*bromomethylpyridine Hydrobromide*.—5-Hydroxy-2-methyl-6-hydroxymethylpyridine (0·3 g.) was dissolved in 60% hydrobromic acid (20 c.c.) and boiled for 10 minutes under reflux. The resulting solution was evaporated to *ca.* 5 c.c. and cooled. Thick white prisms of 5-*hydroxy*-2-*methyl*-6-*bromomethylpyridine hydrobromide* crystallised out. They were collected, washed with acetone and ether, and dried; m. p. 224° (decomp.). Yield, 0·5 g. (Found: N, 5·0; Br, 56·9. C_7H_8ONBr,HBr requires N, 4·95; Br, 56·5%). When the compound (0·4 g.) was recrystallised from a small quantity of water, white needles of 5-*hydroxy*-2-*methyl*-6-*hydroxymethylpyridine hydrobromide* (0·23 g.) separated; m. p. 164° (Found: N, 6·6; Br, 36·1. $C_7H_9O_2N,HBr$ requires N, 6·4; Br, 36·4%).

5-*Methoxy*-2-*methyl*-6-*methoxymethylpyridine*.—5-Hydroxy-2-methyl-6-hydroxymethylpyridine (5·5 g.) was dissolved in methyl alcohol (50 c.c.) and diazomethane (prepared from 20 g. of nitrosomethylurea) in ether (250 c.c.) was added. Next day the solvents were evaporated. The oily product, 5-methoxy-2-methyl-6-methoxymethylpyridine, solidified on standing. Yield, 6·0 g. The *picrate*, recrystallised twice from water, formed light orange long needles, m. p. 140° (Found: N, 14·0. $C_{15}H_{16}O_9N_4$ requires N, 14·1%).

3-*Methoxy*-6-*methylpicolinic Acid*.—5-Methoxy-2-methyl-6-methoxymethylpyridine (3·4 g.) was dissolved in 1·5% potassium hydroxide solution (150 c.c.) and potassium permanganate (4·3 g.) in water (200 c.c.) was added in the course of 6 hours. The solution was left overnight, filtered, neutralised with sulphuric acid, acidified with acetic acid, and concentrated, and the pale green cupric salts of the products of oxidation were precipitated by addition of cupric acetate. The precipitate was collected, washed with water, decomposed with hydrogen sulphide, and the filtrate evaporated to dryness. Yield, 1·3 g. 3-*Methoxy*-6-*methylpicolinic acid* was extracted with hot light petroleum or chloroform, and crystallised on cooling in long transparent needles which had a faint aromatic smell and became opaque on drying at 90°. It was readily soluble in water, insoluble or sparingly soluble in most organic solvents. Recrystallised from light petroleum or chloroform it had m. p. 104° (Found: C, 57·7; H, 5·5; N, 8·2; equiv. by titration, 165. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%; equiv., 167).

3-*Hydroxy*-6-*methylpicolinic Acid*.—3-Methoxy-6-methylpicolinic acid (0·25 g.) was boiled under reflux for 3 hours with 60% hydrobromic acid (25 c.c.). The solution was concentrated to *ca.* 5 c.c., neutralised with 10% sodium carbonate solution, and acidified with acetic acid, and the pale-green cupric salt precipitated with cupric acetate. The salt was collected, decomposed with hydrogen sulphide, and the aqueous solution evaporated. The acid, recrystallised from water, had m. p. 228° (decomp.). Yield, 0·06 g. It gave a reddish-yellow colour with ferrous sulphate, and a cherry red with ferric chloride

(Found: C, 55·1; H, 4·7; N, 8·9. $C_7H_7O_2N$ requires C, 54·2; H, 4·5; N, 9·15%). When heated above its m. p. it yielded a sublimate of 5-hydroxy-2-methylpyridine, m. p. and mixed m. p. 160°.

The author wishes to express his thanks to Professor W. E. Garner, F.R.S., for permission to carry out this work and to Mr. H. Whittaker for all laboratory facilities. His thanks are due to Professor Sir John Lennard-Jones, F.R.S., Chief Scientific Officer, Ministry of Supply, for permission to publish. The analysis were done by Drs. S. G. Weiler and F. B. Strauss, Oxford.

ARMAMENT RESEARCH DEPARTMENT, ROYAL ARSENAL, WOOLWICH. [*Received, May 10th,* 1946.]

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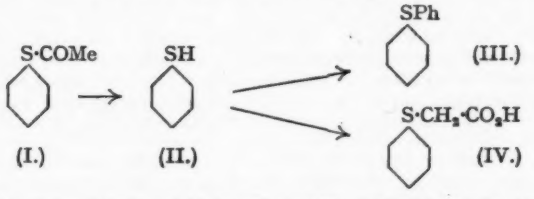
35. *The Addition of Thio-compounds to Olefins. Part II. Reactions of Thiolacetic and Mono-, Di-, and Tri-chlorothiolacetic Acids.*

By J. I. CUNNEEN.

*cyclo*Hexene, 1-methyl*cyclo*hexene, dihydromyrcene, squalene, and rubber * combine additively with the above named thio-acids, the reactions proceeding similarly to, but more easily than, those reported with thiols in Part I. The parallelism noted previously between the ease of thiol addition and the facility of proton removal from the S–H bond as measured by acidity not only extends to thiol acids generally, but also accords with the fact that among the latter themselves the more acid chloro-substituted compounds are the more active addenda. A reactivity order, *cyclo*hexenes > dihydromyrcene > squalene > rubber, is again apparent, but whereas this serves to make the last olefin inert towards thiols, yet thio-acid adducts are readily prepared, and these are of considerable technological interest as oil- and petrol-resistant rubbers.

SINCE thiol acids are a limited group, it is not surprising that their additive reactivity, $>C{:}C<$ $+ R{\cdot}CO{\cdot}SH \longrightarrow >CH{\cdot}\overset{|}{C}{\cdot}S{\cdot}COR$, has been but meagrely explored; in fact, the few such reactions reported have been concerned only with thiolacetic acid. Holmberg (*Arkiv Kemi Min. Geol.*, 1938, **12**, *B*, No. 47) provided the first example in the preparation of β-phenylethyl thiolacetate from styrene in good yield at room temperature. Ipatieff and Friedmann (*J. Amer. Chem. Soc.*, 1939, **61**, 71) studied the addition to propylene, *iso*butylene, *iso*propylethylene, and trimethylethylene at various temperatures and found that, although propylene was inert, the other olefins gave thiolacetates in high yield, the orientation of addition being contrary to Markownikoff's rule. From a comparision of the reactivities of ethanethiol, thiophenol, and thiolacetic acid towards propylene and *iso*butylene, these authors concluded that the last is a less active addendum than the thiols. Sjöberg (*Ber.*, 1941, **74**, 64) treated allyl chloride with the thiol acid at 160°, isolated γ-chloropropyl thiolacetate, and converted this ester into the corresponding thiol by hydrolysis with methyl-alcoholic hydrogen chloride. The addition to some unsaturated acids was followed by Holmberg and Schjånberg (*Arkiv Kemi Min. Geol.*, 1940, **14**, *A*, No. 7), who confirmed Ipatieff and Friedmann's observations concerning the " abnormal " orientation. The present work describes the reaction with *cyclo*hexene, 1-methyl-*cyclo*hexene, dihydromyrcene, squalene, and rubber of thiolacetic and mono-, di- and tri-chloro-thiolacetic acids, the last two *acids* being specially synthesised.

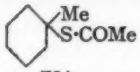
Reactions with Thiolacetic Acid.—On mixing this acid with the liquid olefins named above a violent reaction occurred with the evolution of much heat. The *cyclo*hexene reaction product, isolated by distillation at reduced pressure, was characterised as cyclo*hexyl thiolacetate* (I) in the following way. Alkaline hydrolysis gave the thiol (II), whose sodium salt reacted with iodo-benzene and with bromoacetic acid to give *cyclo*hexyl phenyl sulphide (III) and *cyclo*hexyl-



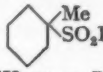
thioglycollic acid (IV), respectively, which are readily identified by means of their crystalline sulphones (see Part I). 1-Methyl*cyclo*hexene gave an analogous *product* which could be either the " normal " (V) or the " abnormal " (VI, R = Me) ester. Again, the product was hydro-

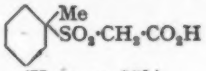
* British and U.S. Patent Specifications pending.

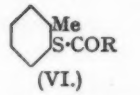
lysed to the *thiol* (VII or VIII), and this converted into the corresponding phenyl sulphide and thioglycollic acid, which were oxidised to the respective crystalline sulphones, m. p. 108° and 96°. The alternative compounds, (IX) and (X) or (XI) and (XII), have been unambiguously


(V.)

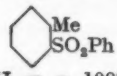
(VII.)

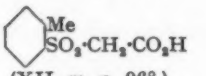

(IX, m. p. 76°.)


(X, m. p. 85°.)


(VI.)

(VIII.)


(XI, m. p. 108°.)


(XII, m. p. 96°.)

differentiated in Part I so that m. p. and mixed m. p. data establish with certainty that the sulphones now obtained are (XI) and (XII), and thus that the original ester is (VI, R = Me).

Dihydromyrcene gave two liquid *thiolacetates* corresponding to the mono- and di-addition compounds (XIII and XIV, R = Me), the latter being readily hydrolysed with alcoholic alkali to the *dithiol* (XV). The squalene reaction *product* when freed from excess of thiol acid in a high

$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CHMe{\cdot}S{\cdot}COR$ (XIII.)

$CHMe_2{\cdot}CH(S{\cdot}COR){\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CHMe{\cdot}S{\cdot}COR$ (XIV.)

$CHMe_2{\cdot}CH(SH){\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CHMe{\cdot}SH$ (XV.)

vacuum was a colourless viscous oil in which 36% of the double bonds had reacted. Reaction between rubber and the thiol acid was investigated in benzene solution. On irradiating such a solution contained in " Pyrex " vessels with a mercury-vapour lamp for a few hours and precipitating the *product* with excess alcohol, a white rubber-like material was obtained in which almost quantitative addition of the thiol acid fragments to the double bonds of the rubber had occurred. The irradiation conditions described appear to be essential for facile reaction. Illumination with a tungsten-filament lamp, heating the reactants to 100—130° in a Carius tube, and leaving a benzene solution in the light of the laboratory for as long as 2 years, in the presence or absence of ascaridole in each case, only induced a fractional amount of the thiol acid to combine. Irradiation with a carbon arc was more successful, but still considerably less efficient than the mercury-vapour lamp. The almost fully saturated rubber derivatives physically resembled the original rubber and gave no detectable indications of cross-linking or molecular degradation. Just as with the simpler olefin analogues, the *rubber thiolacetate* could be hydrolysed to a *thiol*, isolated as a hard fibrous substance. It

(XVI.) $\cdot CH_2{\cdot}CHMe{\cdot}CH(S{\cdot}COR){\cdot}CH_2\cdot$ $\cdot CH_2{\cdot}CHMe{\cdot}CH(SH){\cdot}CH_2\cdot$ (XVII.)

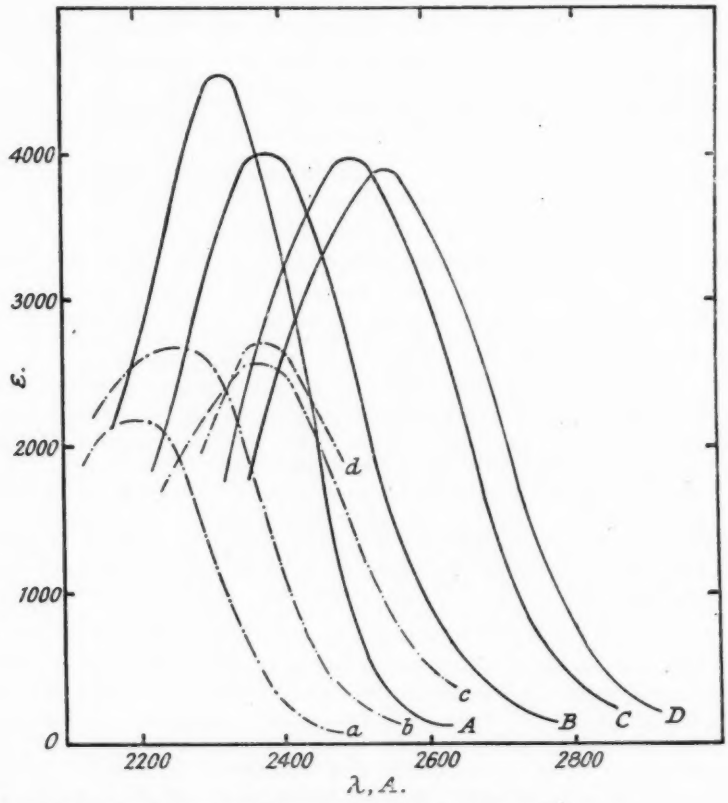
seems certain that the reaction proceeds similarly with all the olefins considered, and therefore that (XVI, R = Me) represents the repeating unit in rubber thiolacetate and (XVII) that in *rubber thiol*, a decision which is confirmed by ultra-violet absorption measurements.

Reactions with Monochlorothiolacetic Acid.—The vigorous reactions of the parent acid with the liquid olefins were repeated with this acid, colourless liquid addition products being obtained in almost quantitative yield. A novel feature of this series, however, is that alkaline hydrolysis of the chlorothiolacetate produces, not thiols, but substituted thioglycollic acids; *e.g.*, cyclo*hexyl chlorothiolacetate* gives *cyclo*hexylthioglycollic acid, obviously owing to interaction between the thiol and chloroacetic acid, the primary hydrolysis products: $C_6H_{11}{\cdot}S{\cdot}CO{\cdot}CH_2Cl$ ($C_6H_{11}{\cdot}SH + CH_2Cl{\cdot}CO_2H$) $\longrightarrow$ $C_6H_{11}{\cdot}S{\cdot}CH_2{\cdot}CO_2H$. Oxidation of the derived thioglycollic acid to its crystalline sulphone of known constitution (Part I) serves to identify the mode of addition to the unsymmetrical olefinic centre in 1-methyl*cyclo*hexene, and proves that addition proceeds abnormally to give the *ester* (VI, R = CH_2Cl). Dihydromyrcene again gave *mono*- and di-adducts (XIII and XIV, R = CH_2Cl), the former separable as a pure compound, but squalene, although reacting vigorously, yielded incompletely saturated products.

In marked contrast to thiolacetic acid, monochlorothiolacetic reacts readily with rubber in benzene solution in the presence of ascaridole in the dark. Irradiation with the mercury-vapour lamp accelerates the reaction considerably, but even so the most convenient preparative method is to leave a solution as intimated above in ordinary daylight for a few days and then to precipitate the rubber derivative either with excess of alcohol or following removal of the benzene by steam distillation. The nature of the peroxide catalyst is somewhat critical. Without added peroxide the reaction is extremely slow; benzoyl peroxide is an almost ineffective pro-

moter, *tert.*-butyl hydroperoxide is much better, but not nearly so good as ascaridole. By limiting the extent of addition a whole series of rubber chlorothiolacetates can be obtained varying from slightly modified rubber to the almost fully saturated hard solid. From the point of view of possible commercial value, the most interesting derivatives were those in which about three-quarters of the double bonds had been saturated : they possess elastic properties comparable with those of the original rubber, are thermally stable at 140°, and have high resistance to solvents such as light petroleum (absorption practically nil) and aviation fuel (absorption 20—30% for a fuel containing 35% of aromatic hydrocarbons). The nature of the reaction and the properties of the products leave no doubt that monochlorothiolacetic

FIG. 1.



Except where otherwise stated, pure cyclo*hexane was used as the solvent.*

a, Thiolacetic acid.
b, Monochlorothiolacetic acid.
c, Dichlorothiolacetic acid.
d, Trichlorothiolacetic acid.
*A, 2-Methyl*cyclo*hexyl thiolacetate.*
B, cyclo*Hexyl chlorothiolacetate.*
C, cyclo*Hexyl dichlorothiolacetate.*
D, cyclo*Hexyl trichlorothiolacetate.*

acid adds to rubber to give an essentially linear polymer with a repeating unit (XVI, R = CH_2Cl), and spectrographic data can again be adduced to confirm this view.

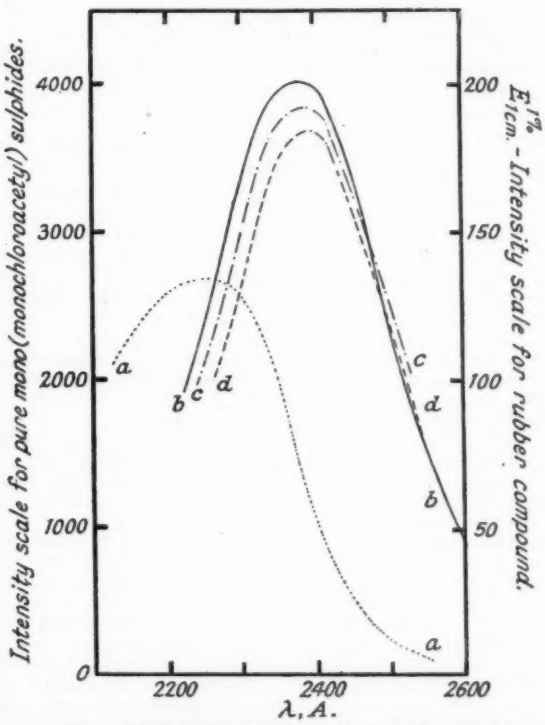
Reactions with Dichlorothiolacetic Acid.—Addition to *cyclo*hexene, dihydromyrcene, and squalene occurred with the usual facility. cyclo*Hexyl dichlorothiolacetate*, $C_6H_{11}\cdot S\cdot CO\cdot CHCl_2$, failed to yield a thiol on hydrolysis, the product being a high-boiling viscous liquid of indefinite constitution, but almost certainly a mixture of α-chloro*cyclo*hexylthioglycollic acid, $C_6H_{11}\cdot S\cdot CHCl\cdot CO_2H$, and bis*cyclo*hexylthioacetic acid, $CH(C_6H_{11}S)_2\cdot CO_2H$, which would result from interaction of the initially formed thiol and dichloroacetic acid. Dihydromyrcene gave mono- and di-adducts again (XIII and XIV, R = $CHCl_2$), of which only the former could be fully purified by distillation. From squalene was obtained an almost colourless gum whose analysis indicated about 75% addition. Rubber reacted just as with monochlorothiolacetic acid, derivatives of varying dichlorothiolacetate content being prepared by leaving benzene

solutions of the reactants plus a little ascaridole in the dark at room temperature for periods varying up to 15 days. The products, undoubtedly containing the units (XVI, R = $CHCl_2$), were slightly harder and less elastic than similarly saturated monochlorothioacetates.

Reactions with Trichlorothiolacetic Acid.—This acid was added to *cyclo*hexene, 1-methyl-*cyclo*hexene, dihydromyrcene, and rubber, *trichlorothiolacetates* being formed readily in each case. *Methylcyclohexyl trichlorothiolacetate* was identified as (VI, R = CCl_3) by careful hydrolysis to a thiol which reacted with iodobenzene to give a phenyl sulphide, this yielding in turn on oxidation the sulphone (XI). Rubber reacted readily in the dark under peroxidic conditions, and more rapidly on irradiation with ultra-violet light. Following the trend described from the monochloro- to the dichloro-thiolacetates, the products were still harder for similar extents of additions, the almost saturated compounds being tough thermoplastic materials resembling gutta-percha.

Absorption Spectra.—In agreement with the spectra of some simple acetyl sulphides already reported in the literature (Sjöberg, *Z. physikal. Chem.*, 1942, *B*, **52**, 909), the ultra-violet absorption curves of the four thioacids and their *cyclo*hexyl esters shown in Fig. 1 are characterised by intense absorption near 2300 A. ($\varepsilon = 3800$), which is evidently associated with conjugation between the carbonyl double bond and the unshared valency electrons of the sulphur atom, as will be more fully discussed elsewhere by H. P. Koch. As the acetyl hydrogen atoms are replaced by chlorine, both acids and esters display successive red shifts that are sufficiently marked to be characteristic of the degree of substitution. The acids absorb relatively less (as regards both wave-length and intensity) than the analogous esters, but the identical spectral type of the two series is in agreement with the infra-red absorption evidence (Sheppard and Sutherland, private communication) that thiolacetic acid has the acetyl hydrogen sulphide structure, $CH_3{\cdot}CO{\cdot}SH$. Comparison of the spectra of the esters prepared from *cyclo*hexene and dihydromyrcene, illustrated in Fig. 2 for the monochlorothiolacetate, and data for the other esters presented in the experimental section, show that both position and intensity of the bands are practically independent of the nature of the hydrocarbon radical attached to the sulphur atom.

FIG. 2.



a, *Monochlorothiolacetic acid.* *b*, cyclo*Hexyl chlorothiolacetate.* *c*, *Dihydromyrcene chlorothiolacetate* (*in dioxan*). *d*, *Rubber chlorothiolacetate* (*in dioxan*).

It is therefore possible to identify and to estimate the composition of the esters obtained from spectroscopically pure rubber by noting the position of the band head and comparing the maximum intensity with the standard intensity of the appropriate $\cdot CH_2{\cdot}CHMe{\cdot}CH(S{\cdot}CO{\cdot}CX_3){\cdot}CH_2\cdot$ unit (X = H or Cl) as derived from the dihydromyrcene adducts (cf. Fig. 2). Such estimations are found to be in reasonable agreement with the results of elementary microanalysis, thus providing a further example of the value of this spectrographic method for both qualitative and quantitative analysis of complex products resulting from the addition of chromophoric groups to rubber and related olefins (cf. Cunneen, Farmer, and Koch, *J.*, 1943, 472).

Discussion.—The additive reactivity of the thiol acids exactly parallels that displayed by the thiols considered in Part I, which have in common the scission of the thio-compound at the S–H bond, the addition of the fragments contrary to Markownikoff's orientation rule, and the marked response to peroxide catalysis. However, the thiol acids are definitely the more powerful reactants, as shown by the vigour of their reactions with the simpler olefins and by their ability to combine with rubber, which seems beyond the power of the thiols. This fact agrees

with the rough correlation pointed out in Part I between the activity of the addenda and the dissociation facility of the S–H links as measured by the acidity of the thio-compound. The correlation, which is completely at variance with Ipatieff and Friedmann's deduction (*loc. cit.*), noticeably extends to the thiol acids series itself in that thiolacetic acid requires added activation by ultra-violet light in order to combine with rubber whereas with the stronger chlorothiolacetic acids combination proceeds readily without this stimulus.

The decrease in reactivity in the olefin series from the *cyclo*hexenes to rubber noted in the thiol reactions is again apparent in the reactions with the thiol acids, although the absolute reaction rates are widely different in the two cases. Attempts to trace the basis of this varying olefinic reactivity form the subject of further investigations in these laboratories.

Thiol acid addition clearly provides a very general method of introducing a substituent R contained in the group ·S·CO·CR into an olefin, and in some cases an easy preparation of thiols and derived thio-compounds such as sulphones. The mild reaction conditions, the absence of side reactions, and the ready control of the extent of addition, are particularly valuable when introducing substituents into long-chain olefins such as rubber with the object of modifying some properties (*e.g.*, resistance to solvents) and at the same time maintaining the high-molecular character responsible for the elastic properties. The extreme susceptibility of rubber to molecular degradation on a scale minute chemically but so often substantial physically, which is such a real barrier to useful modification, appears to have been effectively circumvented in the examples now presented.

Experimental.

Thiolacetic Acid Derivatives.

Preparation of Thiolacetic Acid.—Clarke and Hartmann's method (*J. Amer. Chem. Soc.*, 1924, **46**, 1731) was improved by using sulphuric acid as a catalyst instead of acetyl chloride or bromide, and by separating the thiol acid by distillation through an efficient Fenske column. Light absorption in *cyclo*hexane: $\lambda_{max.}$ 2190 A. ($\epsilon = 2200$).

Reaction of cyclo*Hexene with Thiolacetic Acid.*—A vigorous exothermic reaction occurred on shaking the acid (15·2 g.) with *cyclo*hexene (16·4 g.). After 15 mins., traces of unchanged reactants were removed by distillation at 50° under reduced pressure (water pump). The residue (29·2 g.) was cyclo*hexyl thiolacetate* (I), b. p. 90°/14 mm. (Found: C, 60·1; H, 8·8; S, 20·2. $C_8H_{14}OS$ requires C, 60·6; H, 8·9; S, 20·3%).

cyclo*Hexanethiol* (II). The above ester (20 g.), ethyl alcohol (100 c.c.), and 20% aqueous potassium hydroxide (100 c.c.) were refluxed together for 15 mins. The cooled solution was acidified (acetic acid), and the precipitated thiol collected *via* its ethereal solution and distilled. It (11·4 g.) had b. p. 157°/763 mm. (Found: C, 62·0; H, 10·55; S, 27·9. Calc. for $C_6H_{12}S$: C, 62·1; H, 10·3; S, 27·6%).

cyclo*Hexyl phenyl sulphide* (III). The above thiol (4·6 g.) was dissolved in ethyl alcohol (30 c.c.), and sodium (0·9 g.) added in small pieces. When all the metal had dissolved the alcohol was removed under reduced pressure, leaving solid *cyclo*hexyl sodium sulphide. To this solid, iodobenzene (8·1 g.) and powdered copper (0·05 g.) were added, and the mixture was heated in an oil-bath at 220° for 2 hours. Ether extraction of the cooled mixture gave *cyclo*hexyl phenyl sulphide, b. p. 97—98°/0·05 mm. (Found: C, 75·0; H, 8·4; S, 16·6. Calc. for $C_{12}H_{16}S$: C, 75·0; H, 8·3; S, 16·65%); its identity was confirmed by oxidation by the standard procedure (see Part I) to *cyclo*hexyl phenyl sulphone, m. p. 74°.

cyclo*Hexylthioglycollic acid* (IV). The thiol (II) (4·0 g.) was dissolved in a mixture of ethyl alcohol (22·8 c.c.), potassium hydroxide (1·8 g.), and water (1·2 c.c.), and the solution refluxed under nitrogen. An exactly equivalent solution of bromoacetic acid (4·4 g.) in 50% aqueous ethyl alcohol (19 c.c.) was gradually added, and boiling continued for 4 hours. The mixture was then concentrated to dryness, the solid boiled in water (100 c.c.) for 15 mins., excess of hydrochloric acid added, and the boiling continued for a further 10 mins. The precipitated oil, isolated by chloroform extraction, was the acid (IV) (4·8 g.), b. p. 136°/0·2 mm. (Found: C, 55·0; H, 8·25; S, 18·15; equiv., 180. Calc. for $C_8H_{14}O_2S$: C, 55·2; H, 8·05; S, 18·4%; equiv., 174), again identified by oxidation to its sulphone, m. p. 82° (cf. Part I).

Reaction of 1-*Methyl*cyclo*hexene with Thiolacetic Acid.*—The olefin (9·6 g.) reacted vigourously with the acid (7·6 g.) to give 2-*methyl*cyclo*hexyl thiolacetate* (VI, R = Me), b. p. 110°/14 mm. (16·2 g.) (Found: C, 62·45; H, 9·3; S, 19·0. $C_9H_{16}OS$ requires C, 62·75; H, 9·3; S, 18·6%). Light absorption in *cyclo*hexane: $\lambda_{max.}$ 2315 A. ($\epsilon = 4500$).

2-*Methyl*cyclo*hexanethiol* (VIII). Hydrolysis of the above ester (7 c.c.) as described for the corresponding *cyclo*hexyl homologue gave the *thiol* (4·25 g.), b. p. 165° (Found: C, 64·2; H, 10·7; S, 24·8. $C_7H_{14}S$ requires C, 64·6; H, 10·8; S, 24·6%).

2-*Methyl*cyclo*hexyl phenyl sulphide.* Prepared from the above thiol and iodobenzene as described for the *cyclo*hexyl derivative, this sulphide had b. p. 108°/0·05 mm. (Found: S, 15·2. Calc. for $C_{13}H_{18}S$: S, 15·55%), and readily yielded the corresponding sulphone, m. p. 108°, on oxidation.

2-*Methyl*cyclo*hexylthioglycollic acid.* This sulphide was prepared by treating the thiol (VIII) with bromoacetic acid in the manner previously described, b. p. 130°/0·05 mm. (Found: C, 57·6; H, 8·8; S, 16·7. Calc. for $C_9H_{16}O_2S$: C, 57·4; H, 8·4; S, 17·0%). Oxidation gave the acid sulphone, m. p. 96°.

Reaction of Dihydromyrcene with Thiolacetic Acid.—(a) The olefin (8 g.) was shaken for 30 mins. with the quantity of thio-acid (4·4 g.) required to saturate one double bond. Fractional distillation of the oil so obtained gave: (i) unchanged reactants containing a little sulphide, b. p. <100°/12 mm. (1·6 g.); (ii) *dihydromyrcene monothiolacetate* (XIII, R = Me), b. p. 128°/10 mm. (4·7 g.) (Found: C, 67·35;

H, 10·35; S, 14·6. $C_{12}H_{22}OS$ requires C, 67·3; H, 10·3; S, 14·95%) [light absorption in *cyclo*hexane: $\lambda_{max.}$ 2315 A. ($\epsilon = 4750$); in dioxan, $\lambda_{max.}$ 2330 A. ($\epsilon = 4600$)]; (iii) a mixture of the mono- and di-adducts, b. p. 100—122°/0·1 mm. (2·7 g.).

(b) The reaction was repeated but with excess of thiolacetic acid (17 g., with 14 g. of hydrocarbon). The product on fractionation gave: (i) unchanged reagents, b. p. <80°/0·1 mm. (1·6 g.); (ii) *dihydromyrcene bisthiolacetate* (XIV; R = Me) containing a trace of the monoacetate, b. p. 110—113°/0·1 mm. (4·2 g.) (Found: C, 58·2; H, 9·05. $C_{14}H_{26}O_2S_2$ requires C, 57·85; H, 8·95%); (iii) *dihydromyrcene bisthiolacetate*, b. p. 125°/0·05 mm. (17·8 g.) (Found: C, 57·9; H, 9·0; S, 21·75. $C_{14}H_{26}O_2S_2$ requires C, 57·85; H, 8·95; S, 22·05%) [light absorption in *cyclo*hexane: $\lambda_{max.}$ 2315 A. ($\epsilon = 4750$); in dioxan, $\lambda_{max.}$ 2330 A. ($\epsilon = 4400$)]; (iv) residue (4·1 g.).

Dihydromyrcenethiol (XV). The ester (XIV, R = Me) on alkaline hydrolysis in the usual way gave the parent *dithiol*, a colourless oil, b. p. 128°/25 mm. (Found: C, 58·7; H, 10·6; S, 30·3. $C_{10}H_{22}S_2$ requires C, 58·2; H, 10·7; S, 31·1%).

Reaction of Squalene with Thiolacetic Acid.—The hydrocarbon (2 g.) shaken with the acid (2 g.) for 30 mins. produced a reaction rather less exothermic than that with *cyclo*hexene. Unreacted thiolacetic acid was removed at 100°/10^{-5} mm., leaving a colourless viscous syrup (Found: S, 12·05. Calc. for 36% addition: S, 12·05%).

Reaction of Rubber with Thiolacetic Acid.—(i) Three Pyrex tubes (diam. 1·5 cm.), each containing sol rubber (1 g.), benzene (25 c.c.), and thiolacetic acid (1 c.c.), were sealed in a vacuum, placed 6 in. from a mercury-vapour lamp, and irradiated for 4, 8, and 16 hours, severally. The products isolated by precipitation with ethyl alcohol were similar white rubbers (Found, respectively: C, 71·8; H, 10·1; S, 11·85; C, 69·8; H, 9·8; S, 14·2; C, 67·7; H, 9·55; S, 15·1. 50% addition requires C, 68·0; H, 9·45; S, 15·1%).

(ii) A reaction mixture containing more thio-acid (2·5 c.c.) was irradiated for 6 hours with ultra-violet light, and the product isolated as before (Found: S, 15·5. Calc. for 52% addition: S, 15·5%). Light absorption in dioxan: $\lambda_{max.}$ 2330 A., $E^{1\%}_{1cm.} = 205$; $[C_5H_8.CH_2{\cdot}CO{\cdot}SH]_n$ requires $E^{1\%}_{1cm.} = 10\ \epsilon$/unit $M = 10 \times 4500/144 = 310$; hence amount of addition is 48%.

(iii) An exactly similar reaction mixture to that used in (ii) was irradiated with the mercury-vapour lamp for 16 hours. The product was a hard white solid (Found: C, 58·95; H, 9·0; S, 20·7. Calc. for 86% addition: C, 60·3; H, 8·6; S, 20·7%).

(iv) The reaction mixture as used in (i) was illuminated for 16 hours with a 300-watt tungsten-filament lamp. A white rubber resulted superficially indistinguishable from the starting material (Found: S, 0·6%, corresponding to 1·3% addition).

(v) The reaction mixture as in (i) but containing ascaridole (0·025 g.) was sealed under vacuum and heated in a Carius furnace at 130° for 3 hours. The rubber product again showed little change (Found: S, 1·5%).

(vi) A reaction mixture as in (v) was sealed under vacuum and left in the light of the laboratory for 1½ years. The product showed 26% addition (Found: S, 9·5. Calc.: S, 9·5%).

(vii) The reaction mixture as used in (i) was illuminated with a carbon arc for 45 hours (Found: C, 69·96; H, 9·9; S, 12·8%, corresponding to 39% addition).

(viii) Some experiments were conducted on a larger scale using an annular form of apparatus (external diam. 6 cm., internal diam. 3·5 cm., length 25 cm.) in which the ultra-violet lamp was suspended, the reaction mixture being sealed under vacuum in the outer jacket and cooled with a rapid stream of water. Milled rubber (*M*, 150,000) enabled more concentrated solutions to be used. Rubber (15 g.), dissolved in benzene (150 c.c.) containing thiolacetic acid (15 c.c.), irradiated in a vacuum under these conditions for 9 hours, yielded a white rubber (23 g.) (Found: S, 15·7. Calc. for 53% addition: S, 15·7%). A repeat experiment using 25 c.c. of the acid gave 76% addition (Found: C, 61·8; H, 8·8; S, 19·3. Calc.: C, 62·0; H, 8·8; S, 19·3%).

Rubber thiol (XVII). Finely cut *thiolacetyl rubber* (1 g.) (Found: C, 67·7; H, 9·55; S, 15·1. $C_{12}H_{20}OS$ requires C, 68·0; H, 9·45; S, 15·1%) was dissolved in benzene (35 c.c.) and ethyl alcohol (10 c.c.) containing sodium (0·01 g.). The mixture was shaken for 6 hours at room temperature and then poured into excess ethyl alcohol. The *thiol* was precipitated as a fibrous white solid which was thoroughly washed with water (Found: S, 18·7. $C_{10}H_{18}S$ requires S, 18·8%).

Monochlorothiolacetic Acid Derivatives.

Reaction of cyclo*Hexene with Chlorothiolacetic Acid.*—The acid (22 g.) [b. p. 48°/16 mm. (Arndt and Berkir, *Ber.*, 1930, **63**, 2390). Light absorption in *cyclo*hexane: $\lambda_{max.}$ 2255 A. ($\epsilon = 2650$)] when added to *cyclo*hexene (17 g.) produced an immediate and vigorous exothermic reaction. The product, when freed from starting materials by heating at 90°/14 mm., was cyclo*hexyl chlorothiolacetate*, b. p. 132°/14 mm. (Found: C, 49·95; H, 6·85; S, 16·4; Cl, 18·4. $C_8H_{13}OClS$ requires C, 49·8; H, 6·75; S, 16·6; Cl, 18·4%). Light absorption in *cyclo*hexane: $\lambda_{max.}$ 2380 A. ($\epsilon = 4000$).

Hydrolysis of cyclo*hexyl chlorothiolacetate.* The ester (6·75 g.), ethyl alcohol (35 c.c.), and 20% aqueous potassium hydroxide were refluxed for 4 hours, and after the procedure described for the corresponding thiolacetate, *cyclo*hexylthioglycollic acid (5·3 g.) readily separated, b. p. 120°/0·1 mm. (Found: C, 55·25; H, 8·3; S, 18·25; equiv., 178. Calc. for $C_8H_{14}O_2S$: C, 55·2; H, 8·05; S, 18·4%; equiv., 174). This specimen gave the anthentic sulphone, m. p. 82°, on oxidation.

Reaction of 1-*Methyl*cyclo*hexene with Chlorothiolacetic Acid.*—Reaction between the hydrocarbon (9·6 g.) and the acid (11 g.) proceeded vigorously to give 2-*methyl*cyclo*hexyl chlorothiolacetate* (VI, R = CH_2Cl), b. p. 137°/11 mm. (18·7 g.) (Found: S, 14·85; Cl, 18·5. $C_9H_{15}OClS$ requires S, 15·5; Cl, 17·2%).

Hydrolysis of 2-*methyl*cyclo*hexyl chlorothiolacetate.* The ester, hydrolysed as described for the *cyclo*hexene derivative, gave 2-methyl*cyclo*hexylthioglycollic acid, b. p. 129°/0·05 mm. (Found: C, 57·45; H, 8·65; S, 16·95; equiv., 184. Calc. for $C_9H_{16}O_2S$: C, 57·4; H, 8·4; S, 17·0%; equiv., 186), identified by its crystalline sulphone, m. p. 96°.

Reaction of Dihydromyrcene with Chlorothiolacetic Acid.—The hydrocarbon (10 g.) was shaken with the acid (5·5 g.) for 15 mins. Distillation of the product gave the following fractions: (i) unchanged reactants, b. p. <100°/14 mm. (3·7 g.); (ii) *dihydromyrcene chlorothiolacetate* (XIII, R = CH_2Cl), b. p. 99°/0·1 mm. (9·2 g.) (Found: C, 57·35; H, 8·4; S, 12·7; Cl, 13·65. $C_{12}H_{21}OClS$ requires C, 58·1; H, 8·6; S, 12·4; Cl, 14·2%) [light absorption in dioxan: $\lambda_{max.}$ 2385 A. (ϵ = 3850)]; (iii) mainly dihydromyrcene bischlorothiolacetate contaminated with some of the mono-adduct, b. p. 108—174°/0·1 mm. (Found: C, 49·8; H, 7·0; Cl, 19·0. Calc. for mixture of 77% di-adduct and 23% mono-adduct: C, 49·4; H, 7·1; Cl, 18·5%).

Reaction of Squalene with Chlorothiolacetic Acid.—Squalene (10 g.) was shaken with the acid (17 g.) for 30 mins., the exothermic reaction then having ceased. Unreacted acid was removed in a vacuum (10^{-5} mm.) at 100° leaving a pale green, viscous syrup evidently consisting of a mixture of squalene chlorothiolacetates (Found: S, 15·8; Cl, 17·2. Calc. for 74% addition: S, 15·8; Cl, 17·3%).

Reaction of Rubber with Chlorothiolacetic Acid.—The following are a representative selection of the many experiments carried out with rubber and this acid. (i) A solution of sol rubber (1 g.), benzene (25 c.c.), monochlorothiolacetic acid (1·5 c.c.), and ascaridole (0·05 g.) was sealed under vacuum and illuminated for 6 hours with the mercury-vapour lamp. The product precipitated by ethyl alcohol was a hard white solid (2·2 g.) (Found: C, 48·7; H, 6·6; S, 17·1; Cl, 19·0. Calc. for 88% addition: C, 49·1; H, 6·4; S, 17·1; Cl, 19·0%). (ii) A reaction mixture similar to that used in (i) was evacuated and left in the dark at room temperature for 7 days. The product showed only 58·5% addition (Found: S, 13·75; Cl, 15·6. Calc.: S, 14·1; Cl, 15·65%). Light absorption in dioxan, $\lambda_{max.}$ 2390 A., $E^{1\%}_{1\,cm.}$ = 180. $[C_5H_8Cl{\cdot}CH_2{\cdot}CO{\cdot}SH]_n$ requires $E^{1\%}_{1\,cm.}$ = 10ϵ/unit $M = 10 \times 3850/178{\cdot}5 = 216$, and hence amount of addition is 65·5%. Imbibition of aviation fuel *, 40%. (iii) Five tubes each containing milled rubber (M, 150,000) (1 g.), benzene (10 c.c.), monochlorothiolacetic acid (1 c.c.), and ascaridole (0·05 g.) sealed in a vacuum were kept at room temperature for 4, 6, 10, 18 and 34 days, severally. The products were precipitated and dried, and then had the properties and analytical values given in the table. (iv) The catalytic activity of different peroxides was investigated as follows. To one of four tubes containing the basic reaction mixture as in (iii) was added ascaridole, to another benzoyl peroxide, to the third *tert.*-butyl hydroperoxide, and no addition was made to the fourth. These tubes were sealed under vacuum and kept at room temperature in the dark for 4 days.

The amounts of aviation fuel imbibed by the respective products, isolated in each case by alcohol precipitation, are shown in the table, and since the imbibition varies inversely as the extent of thio-acid addition the catalytic activities of the various peroxides in promoting this addition are clearly seen. Other series of experiments carried out with different peroxide concentrations all showed the same order.

Reaction time, days.	Catalyst.	S, %.	Cl, %.	Liquid imbibed, %. Light petroleum (b. p. 40—60°).	Liquid imbibed, %. Aviation fuel.
4	Ascaridole	12·5	14·3	5	53
6	,,	13·1	15·1	2	43
10	,,	15·5	17·4	1	36
18	,,	15·9	18·0	—	27
34	,,	16·0	17·9	—	24
4	,,	12·5	14·3	5	53
4	(None)	—	—	—	(Product dissolved)
4	Benzoyl peroxide	—	—	—	190
4	*tert.*-Butyl hydroperoxide	—	—	—	72

(v) Larger-scale experiments were carried out in the following way. Milled rubber (50 g.) was dissolved in benzene (500 c.c.) containing monochlorothiolacetic acid (36 c.c.) and ascaridole (2·5 c.c.), and the solution kept in the absence of air at room temperature and in the dark for 15 days. After removal of the benzene by steam-distillation, the product which separated was washed with ethyl alcohol and dried (Found: C, 56·45; H, 7·3; S, 13·2; Cl, 15·3. Calc. for 56% addition: C, 56·0; H, 7·4; S, 13·8; Cl, 15·3%). Imbibition of aviation fuel, 50%.

Dichlorothiolacetic Acid Derivatives.

Preparation of Dichlorothiolacetic Acid.—Arndt and Berkir's method (*loc. cit.*) for the preparation of monochlorothiolacetic acid was adapted to the present synthesis. A rapid stream of dry hydrogen sulphide was passed through a cooled (0°), well-stirred solution of dichloroacetyl chloride (500 g.) and powdered dry aluminium chloride (10 g.) until the evolution of hydrogen chloride had ceased (6—7 hours). Distillation of the reaction mixture yielded *dichlorothiolacetic acid* as a pale green liquid, b. p. 56°/16 mm. (315 g.) (Found: C, 16·55; H, 1·8; S, 21·65; Cl, 49·4. $C_2H_2OCl_2S$ requires C, 16·55; H, 1·4; S, 22·05; Cl, 48·9%). Light absorption in *cyclo*hexane: $\lambda_{max.}$ 2365 A. (ϵ = 2550).

Reaction of cyclo*Hexene with Dichlorothiolacetic Acid.*—The usual reaction between the hydrocarbon (25 g.) and the thio-acid (42 g.) proceeded on shaking. cyclo*Hexyl dichlorothiolacetate* was obtained as the sole product, b. p. 148°/12 mm. (63 g.) (Found: C, 42·4; H, 5·5; Cl, 31·9. $C_8H_{12}OCl_2S$ requires C, 42·3; H, 5·3; Cl, 31·3%). Light absorption in *cyclo*hexane: $\lambda_{max.}$ 2495 A. (ϵ = 3950). Hydrolysis with alcoholic alkali afforded an unidentified viscous oil, b. p. >220°/758 mm. No *cyclo*hexanethiol could be isolated.

Reaction of Dihydromyrcene with Dichlorothiolacetic Acid.—The hydrocarbon (8 g.) was shaken for

* Aviation Fuel RDEF/75 containing approximately 35% of aromatic hydrocarbons was used for imbibition tests.

15 mins. with the thio-acid (12 g.). Fractional distillation of the oily product gave: (i) unchanged reactants containing a little acetate, b. p. <100°/0·1 mm. (2·5 g.); (ii) *dihydromyrcene dichlorothiolacetate* (XIII, R = $CHCl_2$) (4·6 g.), b. p. 118°/0·1 mm. (Found: S, 11·3; Cl, 25·1. $C_{12}H_{20}OCl_2S$ requires S, 11·3; Cl, 25·1%) [light absorption in dioxan: $\lambda_{max.}$ 2505 A. (ϵ = 3900)]; (iii) a mixture of mono- and di-adducts (0·8 g.), b. p. 160—180°/0·1 mm. (Found: C, 43·7; H, 5·8; S, 14·2. Calc. for a mixture 38% $C_{12}H_{20}OCl_2S$ and 62% $C_{14}H_{22}O_2Cl_4S_2$: C, 43·7; H, 5·9; S, 13·6%); (iv) residue (12 g.).

Reaction of Squalene with Dichlorothiolacetic Acid.—After the hydrocarbon (2 g.) had been shaken with the thio-acid (4·5 g.) for 30 mins., unreacted acid was removed at 100°/10^{-5} mm., leaving a pale green gum (Found: C, 43·2; H, 5·6; Cl, 29·55. Calc. for 75% addition: C, 43·8; H, 5·6; Cl, 30·0%).

Reaction of Rubber with Dichlorothiolacetic Acid.—(i) A solution of sol rubber (1 g.), benzene (30 c.c.), ascaridole (0·05 g.), and acid (1·5 c.c.) was sealed under vacuum and left in the dark at room temperature for 10 days. The viscosity of the solution increased almost to the point of gelation. The product obtained by precipitation with ethyl alcohol followed by extraction (Soxhlet) with methyl alcohol in an atmosphere of nitrogen for 24 hours was a white rubber (2·5 g.) (Found: C, 44·4; H, 5·5; S, 13·15; Cl, 29·5. Calc. for 71% addition: C, 44·8; H, 5·5; S, 13·3; Cl, 29·5%). This material showed extensive but sluggish elastic behaviour. (ii) Sol rubber (0·5 g.), benzene (20 c.c.), ascaridole (0·02 g.), and the thio-acid (1·0 c.c.) were kept under vacuum for 5 days at room temperature in the dark. The product isolated in the usual way was a white rubber (Found: S, 10·5; Cl, 23·75. Calc. for 44·4% addition: S, 10·7; Cl, 23·75%).

Trichlorothiolacetic Acid Derivatives.

Preparation of Trichlorothiolacetic Acid.—The acid chloride (500 g.), treated in the usual manner, afforded a mixture which on fractional distillation gave: (i) trichloroacetyl chloride containing some of the thio-acid, b. p. 44—50°/11 mm. (85 g.); (ii) *trichlorothiolacetic acid*, b. p. 57°/11 mm. (348 g.), an almost colourless liquid (Found: C, 13·4; H, 0·6; S, 17·55; Cl, 59·7. C_2HOCl_3S requires C, 13·4; H, 0·6; S, 17·8; Cl, 59·3%) [light absorption in *cyclo*hexane: $\lambda_{max.}$ 2375 A. (ϵ = 2700)]; (iii) residue (43 g.).

Reaction of cyclo*Hexene with Trichlorothiolacetic Acid.*—The solution of the olefin (8·2 g.) in the acid (18 g.) was shaken for 15 mins. The resulting oil on distillation gave exclusively cyclo*hexyl trichlorothiolacetate*, b. p. 151°/12 mm. (25·1 g.) (Found: C, 36·95; H, 4·3; S, 12·25; Cl, 40·6. $C_8H_{11}OCl_3S$ requires C, 36·7; H, 4·2; S, 12·25; Cl, 40·75%). Light absorption in *cyclo*hexane: $\lambda_{max.}$ 2540 A. (ϵ = 3900).

Reaction of 1-*Methyl*cyclo*hexene with Trichlorothiolacetic Acid.*—2-*Methyl*cyclo*hexyl trichlorothiolacetate* (VI, R = CCl_3), b. p. 96°/0·1 mm. (Found: C, 39·65; H, 5·15; S, 11·3; Cl, 38·4. $C_9H_{13}OCl_3S$ requires C, 39·2; H, 4·7; S, 11·65; Cl, 38·6%), was prepared in almost theoretical yield from the hydrocarbon and the thio-acid just as described for the *cyclo*hexene derivative. Submitted to the hydrolytic procedure described for *cyclo*hexyl thiolacetates, the ester gave an oil which reacted with iodobenzene to give 2-methyl*cyclo*hexyl phenyl sulphide, b. p. 105°/0·015 mm. (Found: C, 76·0; H, 8·9; S, 15·3. Calc. for $C_{13}H_{18}S$: C, 75·6; H, 8·75; S, 15·55%), identified by its crystalline sulphone, m. p. 108°.

Reaction of Dihydromyrcene with Trichlorothiolacetic Acid.—Reaction of the hydrocarbon (11 g.) and the thio-acid (10 g.) in the usual way, followed by distillation gave: (i) unreacted dihydromyrcene (0·6 g.), b. p. <100°/15 mm., (ii) *dihydromyrcene trichlorothiolacetate* (XIII, R = CCl_3) (12·1 g.), b. p. 119°/0·05 mm. (Found: C, 45·45; H, 6·15; S, 9·7; Cl, 33·3. $C_{12}H_{19}OCl_3S$ requires C, 45·4; H, 6·0; S, 10·1; Cl, 33·6%) [light absorption in dioxan: $\lambda_{max.}$ 2550 A. (ϵ = 3900)]; (iii) a mixture of mono- and di-adducts (0·6 g.), b. p. 120—155°/0·05 mm. (Found: S, 10·25; Cl, 34·5. Calc. for mixture of 90% $C_{12}H_{19}OCl_3S$ and 10% $C_{14}H_{20}O_2Cl_6S_2$: S, 10·45; Cl, 34·5%); (iv) residue (6·4 g.).

Reaction of Rubber with Trichlorothiolacetic Acid.—(i) Sol rubber (1 g.), dissolved in benzene (30 c.c.) containing the thio-acid (1 c.c.; *i.e.*, insufficient to saturate all the double bonds) and ascaridole (0·05 g.), was sealed under vacuum and kept at room temperature for 15 days. The product, isolated by alcohol precipitation, was a white rubber-like material (2·1 g.) (Found: C, 48·1; H, 5·5; S, 9·4; Cl, 31·7. Calc. for 42·5% addition: C, 48·7; H, 5·8; S, 9·4; Cl, 31·2%). (ii) A similar solution but containing twice the amount of thio-acid was kept for 7 days under similar conditions. The product was a hard white solid (Found: S, 11·95; Cl, 39·8. Calc. for 75·6% addition: S, 11·95; Cl, 39·8%). Light absorption in dioxan: $\lambda_{max.}$ 2555 A., $E^{1\%}_{1\,cm.}$ = 140; $[C_5H_8CCl_2{\cdot}CO{\cdot}SH]_n$ requires $E^{1\%}_{1\,cm.}$ = 10 ϵ/unit M = 10 × 3900/248 = 155, and hence amount of addition is 72%. (iii) An exactly similar solution to (ii) was sealed under vacuum in a Pyrex tube (diam. 1·5 cm.), placed 6″ from the mercury vapour lamp, and irradiated for 6 hours. The product was a hard, brittle solid (Found: C, 36·0; H, 4·1; S, 12·8; Cl, 40·2. Calc. for 87·6% addition: C, 36·0; H, 4·0; S, 12·4; Cl, 41·4%).

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BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
48, TEWIN ROAD, WELWYN GARDEN CITY, HERTS.

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36. *The Crystal and Molecular Structure of Certain Dicarboxylic Acids. Part I. Oxalic Acid Dihydrate.*

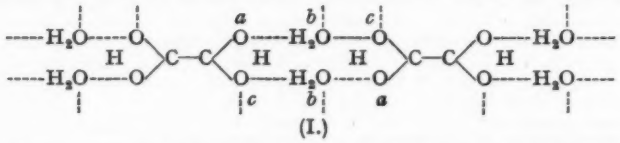
By J. D. Dunitz and J. Monteath Robertson.

The structure of oxalic acid dihydrate is rediscussed in view of results recently obtained by Brill, Hermann, and Peters (*Ann. Physik*, 1942—1943, **42**, 357) which lead to a molecular model with normal or even slightly lengthened carbon–carbon single-bond distance. It is difficult to reconcile the *y* co-ordinates of this structure with the observations. A number of small variations of the structure have been calculated, and some of these show improved agreements. It is concluded that the balance of the evidence is still in favour of a model with a somewhat contracted carbon–carbon bond distance, and with carbon–oxygen distances which are very nearly equal. These findings are consistent with theory, which would appear to demand some double-bond character in the carbon–carbon link, if only to explain the invariance of the coplanar oxalate configuration in many different crystal structures.

The oxalic acid dihydrate structure is redrawn with respect to a different unit cell and space-group description in order to bring out the striking relationship which exists between it and the dihydrates of the acetylenedicarboxylic acid series.

A recent determination of the structure of oxalic acid dihydrate by Brill, Hermann, and Peters (*Naturwiss.*, 1939, 677; *loc. cit.*) gives results which differ in some respects from those found by Robertson and Woodward (*J.*, 1936, 1817). In the present paper these results are rediscussed, and the structure is redrawn (Fig. 1) to bring out the striking relationship which exists between it and the acetylenedicarboxylic acids described in Parts II and III.

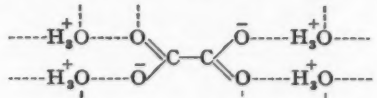
The oxalic acid dihydrate structure may be represented as in (I), with pairs of water molecules connecting the oxalic acid molecules through hydrogen bridges (dotted lines). The bridge *ab* is of special interest because, with a length of about 2·50 A., it appears to be the shortest known



(I.)

hydrogen bridge between oxygen atoms, and it gives rise to an abnormally large isotope effect (expansion of the crystal spacings) when deuterium is substituted for hydrogen (Robertson and Ubbelohde, *Proc. Roy. Soc.*, 1939, *A*, **170**, 221, 241). The other bridges, *bc*, etc., are of weaker type, measuring between 2·8 and 2·9 A. The actual structure in the crystal is more complicated than shown in (I), which is merely a projection diagram. The eight-membered central portion, consisting of two carboxyl groups and two water molecules, is not a closed circuit, the return bridge *bc* connecting to a molecule arranged vertically above the one shown, the whole forming a spiral arrangement extending throughout the crystal. Cross linkings from the water molecule and from one of the carboxylic oxygen atoms also make further connections to other adjoining molecules.

The position of the carboxylic hydrogen atom is still uncertain, and it may well have passed over to the water molecule with the formation of oxonium oxalate, as in (II). Definite

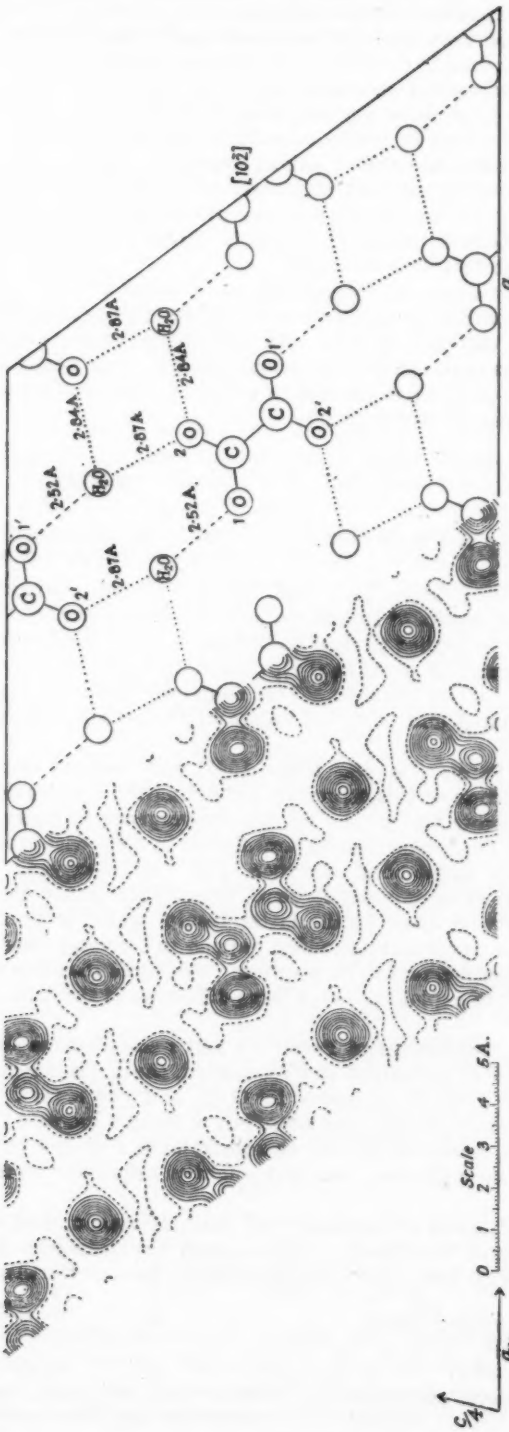


(II.)

experimental evidence is lacking, owing to the difficulty of locating hydrogen atoms in *X*-ray work, but such an arrangement might account for the abnormally short bridge *ab*. In addition, it is expected that a number of other structures, some of them with a double bond between the carbon atoms, will make contributions to the normal state of the molecule (see Robertson, *Trans. Faraday Soc.*, 1940, **36**, 913).

With regard to the expected molecular dimensions in such a situation, some additional evidence is now available since this structure was last discussed (Robertson, *loc. cit.*). A comprehensive electron-diffraction study of the monomers and dimers of certain carboxylic acids has been made by Karle and Brockway (*J. Amer. Chem. Soc.*, 1944, **66**, 574). Their results show that in free acids (monomers) the C–OH and C=O distances in the carboxyl group are different (1·42 and 1·24 A.). On association there is a tendency towards equalisation of

FIG. 1.

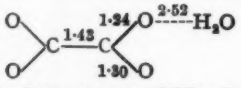


Oxalic acid dihydrate, projected on (010). Each contour line represents a density increment of one electron per A^3., the one-electron line being dotted.

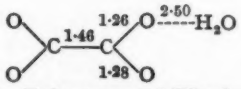
these distances, the values obtained for dimers being 1·36 and 1·25 A. Uncertainties of ± 0·03 or ± 0·04 A. apply to these figures, but the difference of about 0·10 A. for the dimers is apparently significant. It is concluded that the hydrogen atom must remain attached more firmly to one of the partners in the dimer than to the other. In the case of salts, no very precise measurements of these distances are available, but we should expect the ion to display either complete equality of the C–O distances or at least closer equality than is found in the dimers.

If structure (II) is important in oxalic acid dihydrate we would therefore expect the C–O distances to be almost indistinguishable. This is consistent with our *X*-ray results (Robertson and Woodward, *loc. cit.*), which gave the C–O distances as 1·30 and 1·24 A., with a probable error of ± 0·03 or ± 0·04 A. The other molecular dimensions obtained are shown in (III). In the analogous acetylenedicarboxylic acids described in Parts II and III it is also practically impossible to distinguish to two C–O distances.

For the C–C distance in oxalic acid dihydrate we obtained a value of 1·43 A., a contraction form the normal carbon–carbon single-bond value which indicates a considerable amount of conjugation between the carboxyl groups. As the carbon atoms are situated between the higher electron density peaks of the oxygen atoms (Fig. 1), their positions are more uncertain and this figure may be subject to a somewhat larger error. Some contraction from the normal value does, however, appear to be definite.



(III.) Robertson and Woodward.



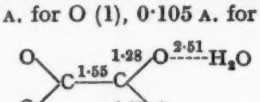
(IV.) Robertson and Woodward, as modified by Booth.

In the meantime, Booth (*Nature*, **1945**, **156**, 51; and private communication) has made a critical examination of the results of Robertson and Woodward (*loc. cit.*) and has derived a set of probable corrections to be applied to their co-ordinates. The application of these corrections leads to the molecular dimensions given in (IV), thus indicating a more symmetrical model with slightly increased carbon–carbon distance. This model also leads to slightly improved agreements between the calculated and observed values of the structure factor (see Experimental section).

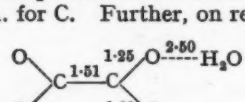
Brill, Hermann, and Peters (*loc. cit.*, 1942—1943) have carried out an independent and extremely careful examination of this structure, extending the observations to smaller spacing planes and applying elaborate corrections for non-convergence of series, etc. The molecular dimensions derived from their final results are shown in (V), with normal or even slightly lengthened carbon–carbon single-bond distance, and carbon–oxygen distances which are slightly different from, and in an opposite sense to, those of Robertson and Woodward (*loc. cit.*). They point out one source of error in the latter results which is probably important, *viz.*, diffraction effects from the oxygen atoms which happen to converge near the carbon atom and may cause an apparent displacement in its position. We agree that this effect may cause some error, but hardly sufficient to explain the very large difference in the carbon–carbon bond length in the two structures.

Examination of Brill, Hermann, and Peters's *x* and *z* co-ordinates shows that they do not differ very much from those of Robertson and Woodward, the displacement of the various atoms being 0·02 A. for H_2O, 0·02 A. for O (1), 0·05 A. for O (2), and 0·06 A. for C. Booth's corrections, mentioned above, are generally in the same sense but of smaller amount than those required by the latter structure. On recalculating the structure factors of the (*h*0*l*) planes from Brill, Hermann, and Peters's co-ordinates, we find slightly improved average agreements (see Experimental section).

It is, however, more difficult to reconcile the Brill, Hermann, and Peters *y* co-ordinates with those of Robertson and Woodward. The required displacements of the atoms are 0·03 A. for H_2O, 0·035 A. for O (1), 0·105 A. for O (2), and 0·10 A. for C. Further, on recalculating the



(V.) Brill, Hermann, and Peters.

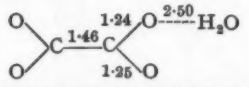


(VI.) Brill, Hermann, and Peters, with Robertson and Woodward's *y* co-ordinates.

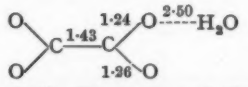
(0*kl*) structure factors, the agreements are considerably worse than found by Robertson and Woodward, the average discrepancies being 18·1% as against 12·4%. If we retain the Brill,

Hermann, and Peters x and z co-ordinates and employ the Robertson and Woodward y co-ordinates, the ($0kl$) discrepancies are reduced to only 13·0%. This composite structure, therefore, gives very good all-round agreements with the observations, and it leads to the molecular dimensions shown in (VI).

The position of the carbon atom is found to have very little effect on the structure-factor calculations, and the two structures shown in (VII) and (VIII), which contain the carbon position as modified by Booth, and the original carbon position of Robertson and Woodward, respectively, are found to give almost equally good general agreements in the structure factor calculations. All the structures (VI)—(VIII) give better agreements than structure (V).



(VII.) Brill, Hermann, and Peters, with Robertson and Woodward's y co-ordinates and Robertson and Woodward–Booth carbon position.



(VIII.) Brill, Hermann, and Peters, with Robertson and Woodward's y co-ordinates and Robertson and Woodward carbon position.

In the Brill, Hermann, and Peters structure (V) the atoms of the acid molecule are strictly coplanar. This fact and also the approximately planar nature of the molecule which is found to hold in the different crystalline modifications of the anhydrous acid, as well as in many oxalates, is a fairly definite indication of double-bond character in the carbon–carbon link. A pure single bond with unrestricted rotation would almost certainly, in some of these structures, lend itself to packing arrangements in which the molecule was not planar. The co-ordinates for structures (III), (IV), and (VI)—(VIII) are found to give certain very slight departures from the strict planar form, the displacements varying from 0·02 to 0·05 A. It is unlikely that any real significance can be attached to these displacements. Very minor adjustments to the co-ordinates could easily be made which would result in strictly planar models.

Our conclusions from this discussion cannot be very definite. The balance of the evidence appears to us still to favour a model with a somewhat contracted carbon–carbon bond distance, and with carbon–oxygen distances which are very nearly equal. Structures (IV), (VI), and (VII) satisfy the requirements almost equally well, and they are consistent with theory. The co-ordinates of structure (VII), which we may provisionally accept as most probable, are given in full in the Experimental section. It is quite clear, however, that questions of finer detail, such as the exact equality or otherwise of the carbon–oxygen distances, can only be settled by a very careful and comprehensive three-dimensional Fourier analysis of all the data. In the two-dimensional projections (*e.g.*, Fig. 1) there is always a considerable lack of resolution and fore-shortening of certain distances owing to the inclination of the molecular plane to the projection plane. In Fig. 1 this inclination is about 29°.

Relation with the Acetylenedicarboxylic Acids.—The similarity between oxalic acid and the acetylenedicarboxylic acids is not at first obvious from the monoclinic cell dimensions, but if the a and c axes of oxalic acid dihydrate are re-named to make the space-group description $P2_1/a$ with acute β angle of 76·6°, the relationship becomes clearer. We shall therefore make this change in our subsequent references to the oxalic acid dihydrate structure, which was formerly described (Zachariasen, *Z. Krist.*, 1934, **89**, 442; Robertson and Woodward, *loc. cit.*) as $P2_1/n$ with $a = 6·12$, $b = 3·60$, $c = 12·03$ A., $\beta = 106·2°$. The new cell dimensions of oxalic acid dihydrate in comparison with those of the dihydrates of the acetylenedicarboxylic acid series are then as given in Table I.

TABLE I.

	Space-group.	a.	b.	c.	β.	c' [10$\bar{2}$].*	β'.
$C_2H_2O_4.2H_2O$	C_{2h}^5–$P2_1/a$	11·88	3·60	6·12	76·5°	14·94	127·2°
$C_4H_2O_4.2H_2O$	C_{2h}^5–$P2_1/a$	11·05	3·86	7·98	98·0	20·64	130·0
$C_6H_2O_4.2H_2O$	C_{2h}^6–$I2/c$	11·15	3·75	20·18	107·0	25·75	131·5

The a and b axial lengths remain fairly constant, but there is a progressive increase in the c axis and in the angle β as further carbon atoms are added to the chain. The directions of these chains with their pairs of connecting water molecules are roughly along the [10$\bar{2}$]* axis in each case, as will be clear from Fig. 2 which shows the relative dimensions of the unit cells of the

* For oxalic acid dihydrate this direction is [102] if the conventional obtuse β angle is adopted, and for diacetylenedicarboxylic acid dihydrate it is [10$\bar{1}$] owing to the doubling of the c axis.

three crystals and the approximate positions of the atoms projected on to the (010) planes. The chain axis is obviously the most important crystal and molecular direction, but it is not convenient to adopt it as a crystallographic axis, because such a description would lead to a cell centred on the (010) face and this would not be a true unit cell in the monoclinic system. In Fig. 2 the broken line outlines the true unit cells (a, c, and β) whereas the full line gives the

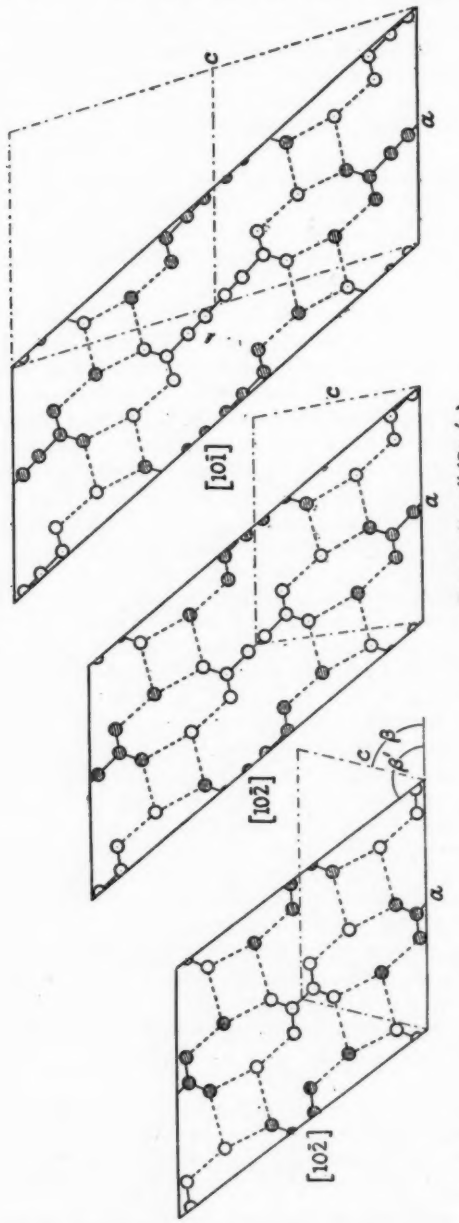


FIG. 2.

Unit cells and atomic arrangement in oxalic acid dihydrate, acetylenedicarboxylic acid dihydrate, and diacetylenedicarboxylic acid dihydrate. The shaded atoms differ from the corresponding unshaded atoms by a reflection across (010) and a translation of b/2.

-·-·- *True unit cell* ($P2_1/a$).
——— *Pseudo-cell.*

pseudo-cells of double area (a, [10$\bar{2}$], and β'). These latter cells give the best description of the molecular structure because [10$\bar{2}$] is then the only substantial variable. The expansion along this axis is approximately that required to accommodate the extra pairs of triply-linked carbon atoms. These double cells also give the clearest pictures of the atomic arrangement, and they will be used in our subsequent diagrams.

Experimental.

Various positions for the atoms, differing by small amounts from those previously given (Robertson and Woodward, *loc. cit.*) were tested. The calculations were confined mainly to the (*h*0*l*) and (0*kl*) structure factors. The greatest uncertainties in these calculations probably lie in the values adopted for the atomic (f) scattering curves. For the present purpose of comparing slightly differing structures we have adopted a purely empirical basis, and have derived the best average f-curve for all the atoms considered together, but with the coefficient for carbon taken at 60% of that for oxygen. Details of the data used have already been given (*idem, ibid.*).

The results of these calculations are summarised in Table II for the molecular models (III)—(VIII) as well as for Zachariasen's original structure (*loc. cit.*). The discrepancy is expressed in each case as

$$\frac{\Sigma\,(|F_{obs.}| - |F_{calc.}|)}{\Sigma\,|F_{obs.}|}$$

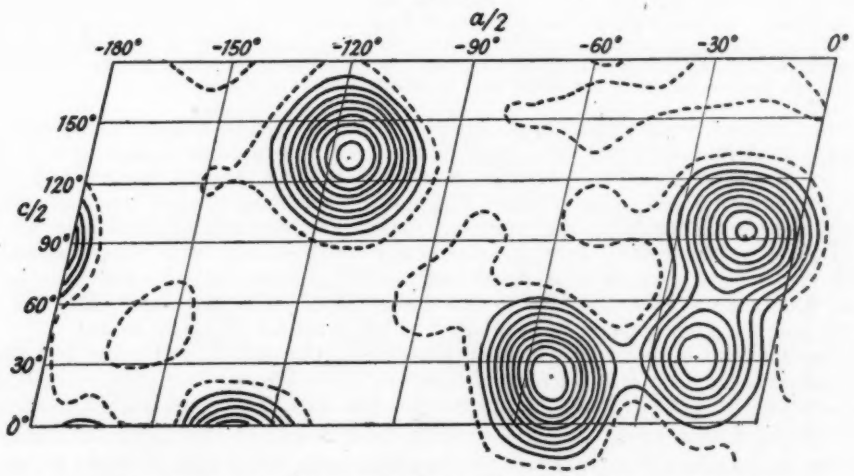
In spite of the uncertainties and assumptions involved in the atomic scattering factors, these discrepancies are probably the best means available for attaching a figure of merit to the various structure models.

Table II.

	Discrepancy, %.	
	(*h*0*l*) including (00*l*).	(0*kl*) without (00*l*).
Zachariasen's structure	15·6	20·7
Structure (III), R.W.	12·4	12·4
Structure (IV), R.W.–Booth	11·3	12·5
Structure (V), B.H.P.	10·0	18·1
Structure (VI), B.H.P. with R.W. *y* co-ords.	10·0	13·0
Structure (VII), do. but with R.W.–Booth carbon	10·0	13·0
Structure (VIII), do. but with R.W. carbon	10·1	13·0

It is our general experience that the residual discrepancy is never better than about 10% when spherically symmetric scattering functions for the atoms are employed. It seems probable that this

Fig. 3.



Co-ordinates of structure (VII) *plotted on the asymmetric crystal unit.*

residual is largely due to the distribution of electron density in the direction of the bonds between the atoms, which is not allowed for in the scattering function; as well as, of course, to some inaccuracies in the experimental intensity measurements.

It is clear that a number of these structures (which only differ from each other very slightly) give almost equally good agreements with the observed data. Structure (VII) has been selected as being perhaps the most probable. Its monoclinic crystal co-ordinates are given in Table III (A) for the space-group description $P2_1/n$ and in Table III (B) for the description $P2_1/a$, and these positions are marked with small crosses on the contour map of the asymmetric crystal unit in Fig. 3. The water molecule which is included in the asymmetric unit in these descriptions is the one most closely bound to the carboxyl group. In former descriptions (Zachariasen, *loc. cit.*; Robertson and Woodward, *loc. cit.*) the other water molecule, derived by the operation 2_1, was included instead.

TABLE III.

Co-ordinates referred to monoclinic crystal axes. Centre of symmetry as origin.

Atom.	x, A.	y, A.	z, A.	$2\pi x/a$.	$2\pi y/b$.	$2\pi z/c$.
(A) Space-group C_{2h}^5–$P2_1/n$. Unit cell $a = 6{\cdot}12$, $b = 3{\cdot}60$, $c = 12{\cdot}03$ A., $\beta = 106{\cdot}2°$.						
C	−0·238	0·120	0·618	− 14·0°	12·0°	18·5°
O (1)	0·507	−0·205	1·778	29·8	−20·5	53·2
O (2)	−1·342	0·770	0·4355	− 78·9	77·0	13·0
H_2O	−0·276	0·390	3·874	− 16·2	39·0	115·9
(B) Space-group C_{2h}^5–$P2_1/a$. Unit cell $a = 11{\cdot}88$, $b = 3{\cdot}60$, $c = 6{\cdot}12$ A., $\beta = 76{\cdot}5°$.						
C	−0·611	0·120	0·553	−18·5°	12·0°	32·5°
O (1)	−1·757	−0·205	0·398	− 53·2	−20·5	23·4
O (2)	−0·430	0·770	1·564	− 13·0	77·0	92·0
H_2O	−3·824	0·390	2·248	−115·9	39·0	132·2

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UNIVERSITY OF GLASGOW. [*Received, May 31st,* 1946.]

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37. *The Crystal and Molecular Structure of Certain Dicarboxylic Acids. Part II. Acetylenedicarboxylic Acid Dihydrate.*

By J. D. DUNITZ and J. MONTEATH ROBERTSON.

The crystal and molecular structure of acetylenedicarboxylic acid dihydrate has been determined from the *X*-ray data. The structure is closely analogous to that of oxalic acid dihydrate, in which two water molecules (or probably oxonium ions) connect the carboxyl groups of adjoining molecules by means of strong hydrogen bridges, the whole forming a spiral arrangement which extends throughout the crystal. The molecular and intermolecular distances are indicated in Figs. 1 and 3. The results are strongly in favour of a symmetrical or nearly symmetrical coplanar structure for the molecule, with resonance effects extending throughout its structure. In locating the centres of the carboxyl group of atoms there are many possible sources of error, and uncertainties of about ± 0·04 A. may apply to the carbon–oxygen distances and to the formal single bond adjacent to the triple bond. The length of the triple bond itself (1·19 A.) should be considerably more accurate.

Crystal Data.—Acetylenedicarboxylic acid dihydrate, $C_4H_2O_4{,}2H_2O$; M, 150·1; m. p. (anhydrous) 175° (decomp.); d, calc. 1·469, found 1·470; monoclinic prismatic, $a = 11{\cdot}05 \pm 0{\cdot}03$, $b = 3{\cdot}86 \pm 0{\cdot}01$, $c = 7{\cdot}98 \pm 0{\cdot}02$ A., $\beta = 98{\cdot}0° \pm 0{\cdot}3°$. Absent spectra, $(h0l)$ when h is odd; $(0k0)$ when k is odd. Space-group, $C_{2h}^5(P_{2_1}/a)$. Two molecules per unit cell. Molecular symmetry, centre. Volume of the unit cell, 337·1 A.^{3} Absorption coefficient for *X*-rays ($\lambda = 1{\cdot}54$ A.), $\mu = 14{\cdot}5$ cm.$^{-1}$. Total number of electrons per unit cell = F(000) = 156.

Large, well-formed crystals were easily obtained from water as colourless laths or plates, elongated along the b axis, the largest face being (001). The (201) and (20$\bar{1}$) are usually developed, and the (100) appears occasionally. Other faces are generally absent.

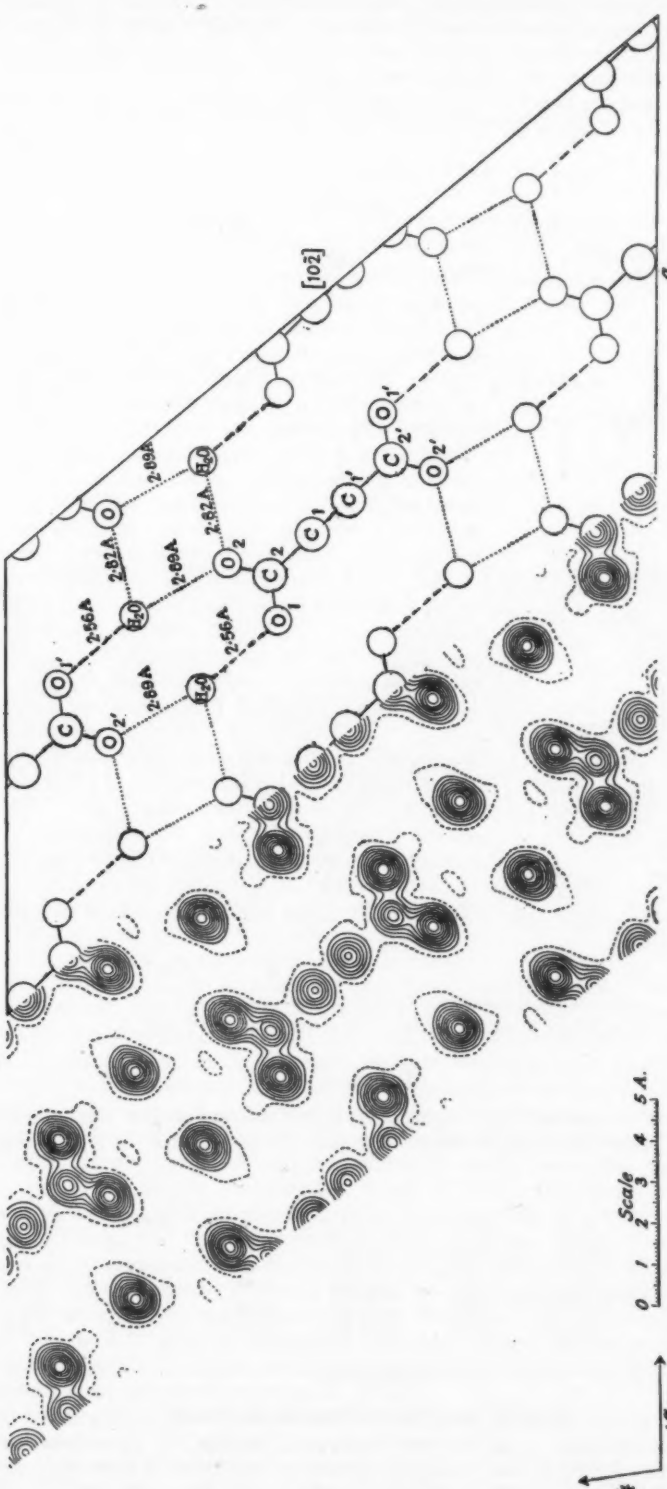
Structure Analysis.—Similarities in the dimensions of the unit cells of oxalic acid dihydrate and acetylenedicarboxylic acid dihydrate (compare Table I, preceding paper) first suggested the main outlines of the structure. In particular, the short b axis and the inclination of the [10$\bar{2}$] axis to the a axis (about 50°) give roughly the direction of the molecular chains, while the increase in length of the [10$\bar{2}$] axis as compared with oxalic acid (2·85 A.) is just about the amount required to accommodate the extra atoms.

A trial model was accordingly set up on these lines and the co-ordinates were refined by three successive Fourier syntheses giving projections of the structure on the (010) plane. The final projection is shown in Fig. 1, from which accurate values of the x and z co-ordinates of all the atoms can be obtained.

The y co-ordinates were obtained by trial and checked by another Fourier projection made along the c axis using the $(hk0)$ structure factors. This is shown in Fig. 2. As only two of the five atoms in the asymmetric unit are separately resolved, the information afforded by this result is not very complete. Nevertheless, Figs. 1 and 2 considered together are sufficient to yield a reasonably precise picture of the whole structure.

Molecular Dimensions and Co-ordinates.—The co-ordinates assigned to the atoms as a

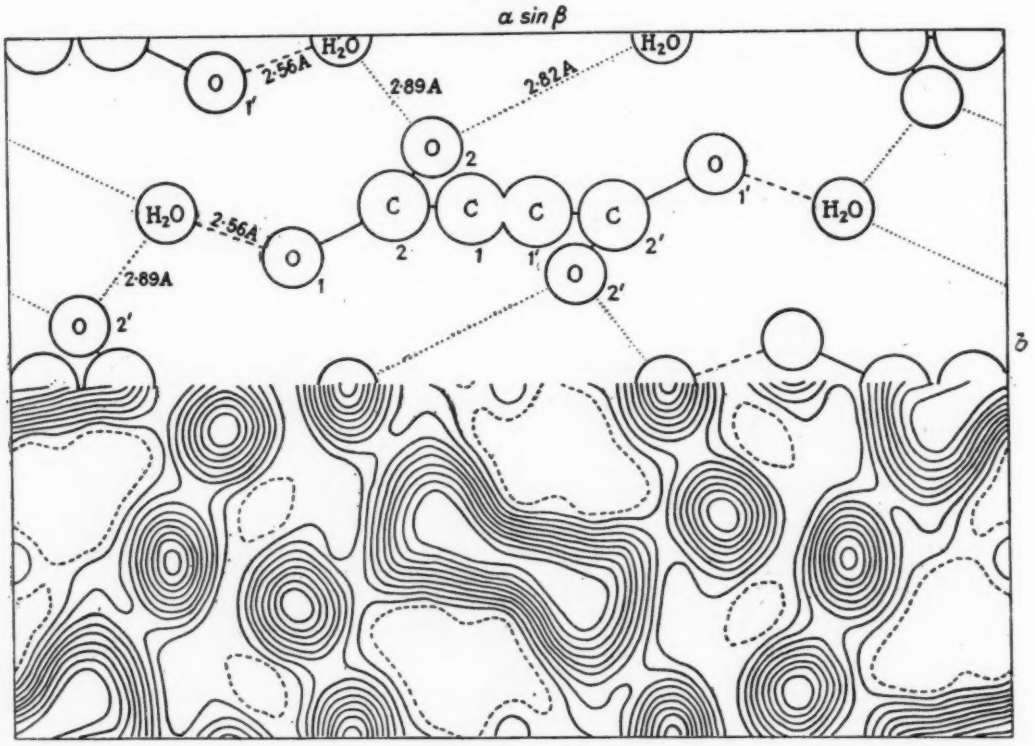
FIG. 1.



Projection along the b *axis, on the (010) plane, covering two unit cells. The plane of the acid molecule is inclined to the projection plane at 33° (ψ_x). Each contour line represents a density increment of approximately one electron per* Å.^{3}*, the one-electron line being dotted.*

result of the final Fourier summations are indicated in Fig. 4 and listed in Table I. These co-ordinates lead to the molecular and intermolecular dimensions given in Figs. 1 and 3, where the atoms of the acid molecule are coplanar and the carbon chain is linear. The orientation of this molecule with respect to the crystal axes is given by the angles in Table II. χ_L, ψ_L, ω_L, χ_M, ψ_M, ω_M and χ_N, ψ_N, ω_N are the angles between the molecular axes L, M, and N, and the crystal axes a, b, and c', c' being perpendicular to a and b. The molecular axis L is the direction

FIG. 2.



Projection along the c *axis. Contour scale as in Fig.* 1.

TABLE I.

Co-ordinates. Centre of symmetry as origin, x, y, z, *are referred to the monoclinic crystal axes.* x′, y, z′, *are rectangular co-ordinates referred to the* a *and* b *crystal axes, and their perpendicular,* c′.

Atom (cf. Fig. 1).	*x*, A.	*y*, A.	*z*, A.	*x*′, A.	*z*′, A.	$2\pi x/a$.	$2\pi y/b$.	$2\pi z/c$.
C (1)	−0·36	−0·02	0·43	−0·42	0·42	− 11·6°	− 2·0°	19·3°
C (2)	−1·22	−0·07	1·46	−1·42	1·44	− 39·6	− 6·6	65·6
O (1)	−2·35	0·50	1·27	−2·53	1·26	− 76·7	47·1	57·3
O (2)	−0·78	−0·70	2·52	−1·13	2·49	− 25·5	−65·3	113·6
H_2O	−3·77	0·00	3·16	−4·21	3·13	−122·9	0·0	142·6

TABLE II.

Orientation of the molecule in the crystal.

$\chi_L = 134·5°$, $\cos\chi_L = -0·7004$	$\chi_M = 52·3°$, $\cos\chi_M = 0·6114$	$\chi_N = 68·4°$, $\cos\chi_N = 0·3680$
$\psi_L = 92·0°$, $\cos\psi_L = -0·0349$	$\psi_M = 123·0°$, $\cos\psi_M = -0·5446$	$\psi_N = 33·0°$, $\cos\phi_N = 0·8380$
$\omega_L = 44·5°$, $\cos\omega_L = 0·7128$	$\omega_M = -55·0°$, $\cos\omega_M = 0·5741$	$\omega_N = 66·2°$, $\cos\omega_N = 0·4028$

of the carbon chain; M lies in the plane of the molecule and is perpendicular to L; N is the normal to the molecular plane. The co-ordinates of the atoms with respect to these molecular axes are given in Table III.

TABLE III.

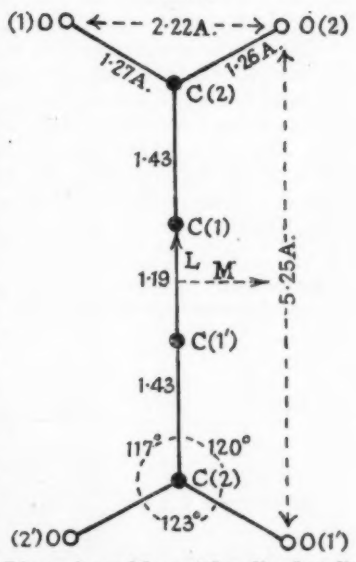
Co-ordinates of atoms with respect to molecular axes.

Atom	C_1	C_2	O_1	O_2
L, A.	0·595	2·025	2·655	2·595
M, A.	0	0	−1·10	1·12

DISCUSSION OF RESULTS.

It is immediately clear that the same kind of structure exists in crystals of oxalic acid dihydrate, acetylenedicarboxylic acid dihydrate, and, with minor space-group deviations noted in Part III, in diacetylenedicarboxylic acid dihydrate. In all these structures the two molecules of water of crystallisation and the carboxyl groups at each end of the carbon chains are the common factors which determine the manner in which the crystals are built. The relative positions of the oxygen atoms display quite a remarkable constancy in all these structures, a fact which is well illustrated in Fig. 2 of the previous paper. Although the carbon chain is different for each acid this has very little influence on the forces holding the molecules together in the crystal. The only effect is a slight tightening in the lateral packing on passing from oxalic acid to the acetylene acids, indicated by a decrease of about 0·8 A. in the length of the a axis, and possibly some weakening of packing in the direction of the b axis, which shows a small increase in length from 3·60 A. in oxalic acid to 3·86 and 3·75 A. in the two acetylene acids.

FIG. 3.



Dimensions of the acetylenedicarboxylic acid molecule.

As in the oxalic acid structure, a very short hydrogen bridge exists between the oxygen atom O(1) and the water molecule (Fig. 1). This bridge measures 2·56 A., as against 2·51 A. in oxalic acid, and it is the only hydrogen bridge formed by the oxygen atom O(1), the next nearest approach of a water molecule being over 4 A. The other carboxylic oxygen atom O(2) forms two hydrogen bridges of a much weaker type (2·89 and 2·82 A.) with two other water molecules. Each water molecule in turn forms three hydrogen bridges (2·56, 2·82, and 2·89 A.) to surrounding carboxylic oxygen atoms. It is clear, therefore, that each water molecule engages three hydrogen atoms; but whether these three hydrogen atoms should all be regarded as permanently attached to the water molecule, with the formation of an oxonium ion, is a question that cannot be answered definitely from the experimental evidence before us. If the mechanism of the hydrogen bridge is entirely electrostatic, this may be the case. On the other hand, there is obviously a great difference in quality between the three bridges, one of them being 0·3 A. shorter than the other two. The possibility of the ready transfer of a hydrogen atom across the short bridge is a factor which must obviously receive serious consideration. From the purely electrostatic point of view, this transfer will have taken place from the hydroxyl oxygen of the carboxyl group, leaving this oxygen with a negative charge and so accounting for the extra short hydrogen bridge. This view receives support from the work of Brill, Hermann, and Peters (*Ann. Physik*, 1942—1943, **42**, 357), who claim to have differentiated the carbon–oxygen bond lengths in oxalic acid dihydrate and identify the oxygen atom O(1) which gives the short hydrogen bridge as the hydroxyl oxygen. In our present results we are not able to distinguish the two oxygen atoms as giving measurably different carbon–oxygen bond lengths in the acetylene acids, and in our former work on oxalic acid (see previous paper) this matter is also in doubt.

With regard to the general arrangement of the molecules in the crystal, it should be observed that the acid molecules are not, as might be inferred from Fig. 1, arranged in series of infinite chains linked by hydrogen bridges, but in infinite spirals. The apparently closed ring formed by the atoms H_2O, O(1), C(2), O(2), H_2O, O(1'), C(2'), O(2'), H_2O is actually a spiral, the return

connection leading to a molecule one translation further along the *b* axis, as will be clear from Fig. 2. However, the four-membered ring formed by the weaker bridges, 2·89, 2·82, 2·89, and 2·82 A., is actually a closed circuit as represented in Fig. 1. In these respects the structure is similar to that of oxalic acid dihydrate.

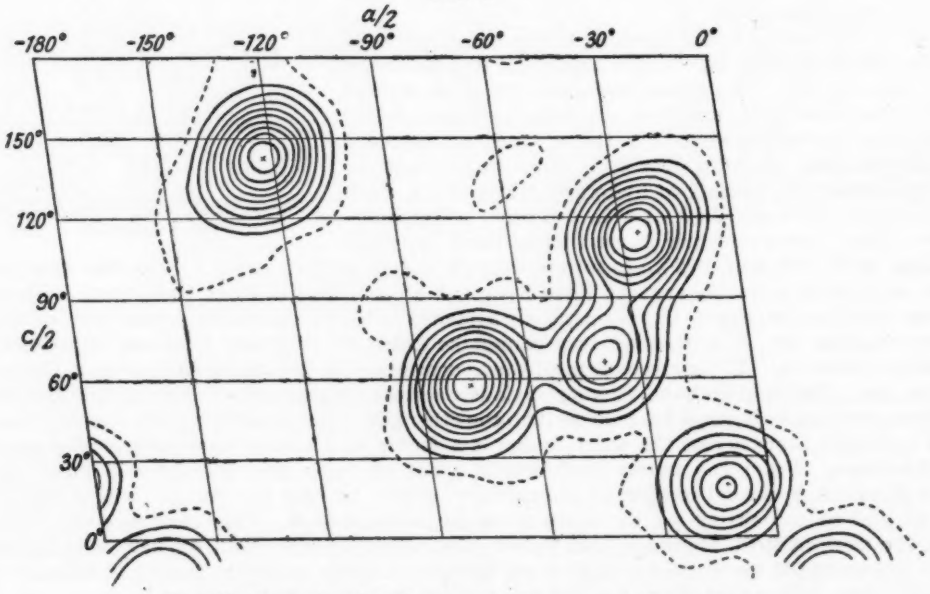
The internal dimensions which we find for the acetylenedicarboxylic acid molecule are indicated in Fig. 3. It is very difficult to make a reliable assessment of limits of accuracy which should be attached to these figures. The considerable divergence between the results of different observers in the case of oxalic acid dihydrate (see previous paper) is a warning that, especially in the case of the carboxyl group of atoms, there are many possible sources of error. In the present analysis we have not attempted any elaborate corrections for diffraction effects due to non-convergence of the series, etc., as the experimental data scarcely seem sufficiently reliable to justify such work. To the data as they stand in Fig. 3 we would attach a possible error of about $\pm$ 0·04 A. for the carbon–oxygen distances, and for the single-bond carbon–carbon distance of 1·43 A. The triple-bond carbon–carbon distance of 1·19 A. should be considerably more reliable than this owing to more favourable resolution, and we would assess the possible error in this case at about $\pm$ 0·02 A.

Our results are strongly in favour of a symmetrical or very nearly symmetrical co-planar structure for the molecule with considerable resonance effects extending throughout its structure. The formal single bond of 1·43 A. adjacent to the triple bond may be compared with the corresponding bond in tolan, where the value obtained was 1·40 A. (Robertson and Woodward, *Proc. Roy. Soc.*, 1938, **164**, *A*, 436), and in diphenyldiacetylene, where the value of 1·44 A. was reported by Weibenga (*Z. Krist.*, 1940, **102**, 193). This bond length and also the somewhat contracted value of 1·19 A. which we find for the triple bond distance are further discussed in Part III.

Experimental.

Preparation, and Determination of Data.—Acetylenedicarboxylic acid was prepared in good yield from $\alpha\beta$-dibromosuccinic acid (*Org. Synth.*, 1938, **18**, 3). Crystals of the dihydrate obtained from

Fig. 4.



Co-ordinates assigned to the atoms in the asymmetric crystal unit.

aqueous solution were usually too large for accurate *X*-ray work, but specimens of suitable dimensions could be cut with a razor blade.

Copper-$K\alpha$ radiation, $\lambda = 1{\cdot}54$, was used throughout, and rotation, oscillation, and moving-film photographs of the principal zones were taken. For the ($h0l$) zone the specimens employed for most of the intensity work had cross-sections normal to the *b* axis of (*a*) 0·29 by 0·33 mm. and (*b*) 0·56 by 0·50 mm. Crystals of the dihydrate smaller than (*a*) tend to decompose by loss of water before completion of the exposure, but with slightly larger crystals the partial dehydration of the surface layers

during experiment does not result in any loss of accuracy. If anything, it is an advantage in so far as it ensures the true mosaic character of the specimen, which is usually assumed. For the (*hk*0) zone a specimen of cross section 0·55 by 0·65 mm. normal to *c* was employed. These various crystals were completely immersed in the *X*-ray beam, and the spectra recorded up to the limit for $\lambda = 1{\cdot}54$ A. on series of moving films. The multiple-film technique (Robertson, *J. Sci. Instr.*, 1943, **20**, 175) was used for correlation of intensities, and the total range covered was about 2000 to 1. Two independent sets of visual estimates were made on the films from one of the *b* rotation crystals, and one set from the

TABLE IV.

Measured and calculated values of the structure factor.

hkl.	sin θ (λ = 1·54).	F, meas.	F, calc.	*hkl.*	sin θ (λ = 1·54).	F, meas.	F, calc.	*hkl.*	sin θ (λ = 1·54).	F, meas.	F, calc.
200	0·141	<1·5	+ 1·5	608	0·941	4	+ 5	12,04	0·979	1·5 *	− 2
400	0·282	11	− 9	607	0·852	<3	+ 1	12,03	0·934	3·5	+ 5·5
600	0·423	7	− 3·5	606	0·768	8·5	−10·5	12,02	0·897	<3	+ 1
800	0·564	9·5	− 9	605	0·691	4·5	+ 7·5	12,01	0·869	5	− 5·5
10,00	0·705	<3·5	− 1·5	604	0·617	<3·5	+ 2	12,0$\bar{1}$	0·843	7·5	− 6·5
12,00	0·845	<3	− 1	603	0·545	10·5	+11·5	12,0$\bar{2}$	0·845	4	− 1·5
				602	0·493	19	+20	12,0$\bar{3}$	0·861	4	+ 3
020	0·399	27	+25	601	0·449	9	+ 9·5	12,0$\bar{4}$	0·886	3·5	+ 2
040	0·798	4	+ 5	60$\bar{1}$	0·423	26·5	−22·5	12,0$\bar{5}$	0·920	3	− 2
				60$\bar{2}$	0·443	17·5	+16·5	12,0$\bar{6}$	0·966	7·5	− 5
001	0·098	5·5	+ 5·5	60$\bar{3}$	0·437	13	−10				
002	0·195	21·5	−16	60$\bar{4}$	0·538	16·5	−14	110	0·212	26·5	+26·5
003	0·293	4·5	+ 1·5	60$\bar{5}$	0·606	18	+15	210	0·245	17	− 7·5
004	0·390	21·5	−25	60$\bar{6}$	0·676	11·5	−13·5	310	0·291	21	+17
005	0·488	11·5	+12	607	0·756	6·5	− 5·5	410	0·346	32·5	−26·5
006	0·586	12	+12	60$\bar{8}$	0·839	<3	+ 0·5	510	0·405	<2	− 3
007	0·683	<3·5	+ 5	60$\bar{9}$	0·926	7	− 3	610	0·467	5	+ 5
008	0·781	8	−10					710	0·532	19·5	−18·5
009	0·879	6	− 6·5	807	0·946	<2	− 1	810	0·598	<2	− 3
00,10	0·976	<1·5	+ 0·5	806	0·873	<3	− 0·5	910	0·665	10·5	+13
				805	0·797	10	+14	10,10	0·733	4·5	+ 5
209	0·912	<2·5	+ 0·5	804	0·731	10·5	+13·5	11,10	0·801	3	− 2·5
208	0·816	6	− 5·5	803	0·673	6·5	− 9	12,10	0·869	<2	+ 1
207	0·718	7·5	+11	802	0·623	4	+ 6·5	13,10	0·937	4	− 3
206	0·623	5	− 8	801	0·588	12·5	−14·5	120	0·406	7	+ 8
205	0·528	17	−22·5	80$\bar{1}$	0·557	23·5	+25·5	220	0·424	5	+ 0·5
204	0·433	20·5	+21·5	80$\bar{2}$	0·574	<3	− 1	320	0·452	20·5	−23
203	0·344	9·5	+ 9	80$\bar{3}$	0·601	9	− 9	420	0·489	2	− 9
202	0·256	33	+32·5	80$\bar{4}$	0·644	13	−12·5	520	0·533	<2	− 2
201	0·183	32·5	+36·5	80$\bar{5}$	0·695	7·5	− 7·5	620	0·581	9	+14·5
20$\bar{1}$	0·162	24	−25	80$\bar{6}$	0·758	4·5	− 4	720	0·635	<2	+ 1
20$\bar{2}$	0·225	27·5	−25	80$\bar{7}$	0·829	4·5 *	− 1·5	820	0·691	4·5	+ 5·5
20$\bar{3}$	0·308	45·5	+47	80$\bar{8}$	0·900	6	+ 5·5	920	0·745	<2	0
20$\bar{4}$	0·397	9	+ 8	80$\bar{9}$	0·977	3·5	− 2	10,20	0·810	<2	− 2
20$\bar{5}$	0·490	7·5	− 5					11,20	0·872	2·5	+ 4
20$\bar{6}$	0·586	3·5	+ 5	10,06	0·978	3	+ 5	12,20	0·935	2	− 2
20$\bar{7}$	0·680	22·5	−27·5	10,05	0·914	<2·5	+ 0·5	130	0·603	2·5 *	− 4·5
20$\bar{8}$	0·778	6·5	− 5·5	10,04	0·854	4	− 4·5	230	0·615	<2	+ 2
20$\bar{9}$	0·876	5	+ 4	10,03	0·801	<3·5	− 3	330	0·635	7	+12·5
20,1$\bar{0}$	0·972	<1·5	+ 0·5	10,02	0·758	<3·5	+ 3	430	0·662	4·5	− 3
				10,01	0·728	7·5	+10·5	530	0·695	3	− 4·5
409	0·961	<2	− 2·5	10,0$\bar{1}$	0·700	5	+ 3	630	0·733	6 *	+ 3
408	0·867	<3	0	10,0$\bar{2}$	0·705	14	−16·5	730	0·775	2·5	+5·5
407	0·776	<3·5	+ 1	10,0$\bar{3}$	0·728	18·5	−19·5	830	0·823	2	− 2·5
406	0·686	4·5	+ 6	10,0$\bar{4}$	0·759	11·5	+ 9·5	930	0·872	2·5	+ 3·5
405	0·599	<3·5	− 3	10,0$\bar{5}$	0·803	<3	0	10,30	0·925	1·5	+ 0·5
404	0·514	17	+21	10,0$\bar{6}$	0·856	<3	+ 0·5	11,30	0·979	<1	0
403	0·437	4	+ 5·5	10,0$\bar{7}$	0·916	<2·5	+ 1	140	0·801	<2	+ 0·5
402	0·367	21	−20·5	10,0$\bar{8}$	0·982	6	− 3·5	240	0·811	4	+ 4·5
401	0·313	40·5	+39·5					340	0·826	2	+ 3
40$\bar{1}$	0·287	3·5	+ 2					440	0·846	<2	− 4·5
40$\bar{2}$	0·322	41·5	+40					540	0·873	2 *	+ 2
40$\bar{3}$	0·380	14·5	−14					640	0·903	<2	+ 2·5
40$\bar{4}$	0·450	16	−14·5					740	0·938	<2	+ 0·5
40$\bar{5}$	0·531	18	−16					840	0·977	<1	+ 1
40$\bar{6}$	0·616	6	− 4								
407	0·705	<3·5	− 2								
40$\bar{8}$	0·794	<3·5	− 0·5								
40$\bar{9}$	0·890	4·5	+ 4								
40,1$\bar{0}$	0·982	6	− 4·5								

other crystal. The mean of these three estimates was accepted as correct. For the *c* rotation similar methods were adopted. Absorption corrections were not employed, as the dimensions of the crystal specimens render them unnecessary. F values were finally derived by the usual formulæ for mosaic crystals and are listed in Table IV. Absolute measurements were not carried out, and the scale of the F values was obtained by correlation with the values finally calculated from the atomic positions found.

Structure Determination.—After preliminary determination of atomic positions by trial, the structure was refined by three successive two-dimensional Fourier syntheses giving projections on (010) and one giving a projection normal to the *c* axis. The usual formulæ for $\rho(x, z)$ and $\rho(x, y)$ were employed. For $\rho(x, z)$ the series were summed at 450 points on the asymmetric crystal unit, the axial sub-divisions being $a/60 = 0{\cdot}184$ A. and $c/30 = 0{\cdot}266$ A. Three-figure methods (Robertson, *Phil. Mag.*, 1936, **21**, 176) were employed, and the positions of the contour lines plotted on a scale of 5 cm. to 1 A. by graphical interpolation from the arrays of summation totals. The final plot of the asymmetric unit for the *b* projection is shown in Fig. 4, and in this diagram the final positions assigned to the atoms are indicated by small crosses.

These co-ordinates are found to be consistent with the molecular model given in Fig. 3, and the orientation listed in Table II. An independent check on the *y* co-ordinates is, of course, obtained from the projection along the *c* axis shown in Fig. 2. From the final co-ordinates (Table I) all the structure factors were recalculated and the results are given in Table IV. For this calculation the composite empirical atomic scattering curve used in the case of oxalic acid dihydrate (Robertson and Woodward, *J.*, 1936, 1817) was again employed, but with the carbon and oxygen coefficients weighted in the ratio 6 to 9, instead of 6 to 10. This alteration, suggested empirically by the data, is probably due to a slightly different form of temperature factor. There is, of course, no theoretical justification for the use of a single *f*-curve for all the atoms. It is employed at present merely because it is found to give a sufficiently good approximation for the purpose on hand. The discrepancy finally obtained, expressed as

$$\frac{\Sigma\,(|\,F_{meas.}\,| - |\,F_{calc.}\,|)}{\Sigma\,|\,F_{meas.}\,|}$$

is 14·9% for the (*h*0*l*) reflections, 25·4% for the (*hk*0) reflections, and 17·5% for all reflections.

The rather large discrepancy in the case of the (*hk*0) reflections is difficult to explain. The expansion of the *b* axis to 3·85 A. as compared with 3·60 A. in oxalic acid dihydrate probably indicates a rather looser form of packing in this direction, and the atomic *f* curves which we have employed in these calculations may not be applicable, owing to differences in the temperature factor. It is clear that we must accept a considerable uncertainty in the *y* co-ordinates of the atoms. This will not, however, have much effect on the dimensions of the carbon chain, which are determined principally from the (*h*0*l*) projection.

In the *b* axis projection the F values for the (80$\bar{7}$) and (12,04) planes, and in the *c* axis projection the F values for the (130), (630), and (540) planes (marked by an asterisk in Table IV), were omitted from the Fourier summations owing to uncertainty of sign. The sign of F (220) is very doubtful, but this term has been included.

We thank the Royal Society for a grant which defrayed the cost of some of the apparatus used in this work, and one of us (J. D. D.) is indebted to the Carnegie Trustees for a Scholarship.

UNIVERSITY OF GLASGOW. [*Received, May 31st*, 1946.]

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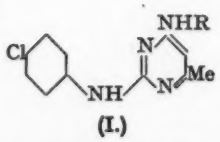
38. *Synthetic Antimalarials. Part XII. Some* 1 : 3 : 5-*Triazine Derivatives.*

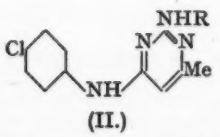
By F. H. S. CURD, J. K. LANDQUIST, and F. L. ROSE.

The series of 2-anilino-4-dialkylaminoalkylamino-6-methylpyrimidines described in Part I (*J.*, 1946, 343), has been extended to corresponding and related 1 : 3 : 5-triazine derivatives. Some of these compounds were prepared by acylation and ring-closure of N^1-aryl-N^5-alkyl-diguanides, others by stepwise reaction of cyanuric chloride with aryl- and alkyl-amines. No compound of the series showed antimalarial activity, and the theoretical implications of this are discussed.

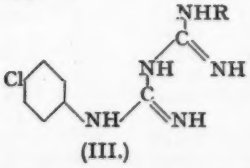
PART I of this series (Curd and Rose, *loc. cit.*) recorded the preparation and discovery of antimalarial activity in substances of which (I; R = $[CH_2]_2{\cdot}NEt_2$) was typical.



(I.)



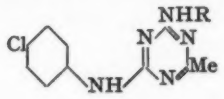
(II.)

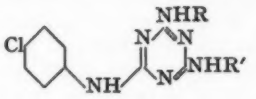


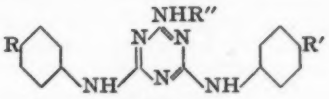
(III.)

Further development of this type has led to still other active structures such as the isomer (II) and the simple diguanides (III; R = alkyl). Consideration of these formulæ suggested the

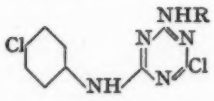
examination of 1 : 3 : 5-triazine analogues, for example, (IV), (V), (VI), and (VII). Not only did these bear an obvious molecular shape relationship to the earlier compounds, but they

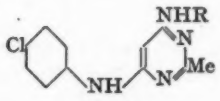

(IV.)


(V.)


(VI.)

appeared at first sight to present those features which we had come to consider essential for positive activity (Part X, Curd and Rose, *J.*, 1946, 729), namely, the existence within the molecule of two independent $-NH-C{=}N-$ systems associated severally with the aryl and the R group. In fact, not one of the many triazine preparations has exhibited any antimalarial

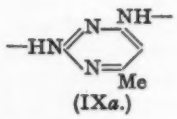

(VII.)

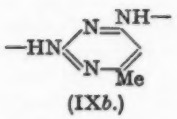

(VIII.)

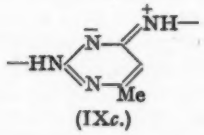
activity, and it is necessary to review our working hypothesis relating structure and biological effect in the light of this result.

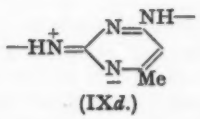
We are not yet prepared to differentiate between the apparent antimalarial significance of prototropic and electromeric phenomena. The amidino-group is such, however, that the two effects are closely interwoven and in the discussion which follows we have confined ourselves to the implications of resonance forms without attempting to define the position of the relevant hydrogen atoms.

On this basis, analysis of the active pyrimidine compounds (I) and (II) shows that, in addition to the Kekulé forms (IX*a*) and (IX*b*), the " independence " of the amidino-groups within the molecules permits the existence of structures such as (IX*c*) and (IX*d*); of these special sig-

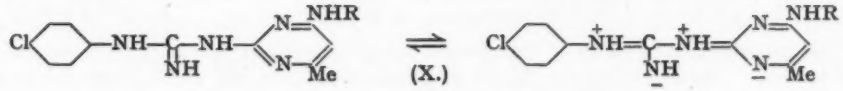

(IX*a*.)

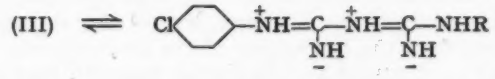

(IX*b*.)


(IX*c*.)


(IX*d*.)

nificance is attached to (IX*d*), in which a conjugated path can be traced through alternate carbon and nitrogen atoms from the one extranuclear nitrogen atom to the other. Similar arrangements can be shown in certain polarised forms of the active guanidinopyrimidine type (X) (Part IV, Curd and Rose, *J.*, 1946, 362) and the diguanide type (XI) (Part X, *loc. cit.*). As with (I) and (II) conjugation extends from the anilino-nitrogen to the nitrogen

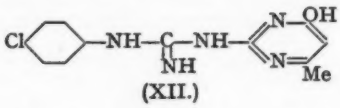

(X.)


(XI.)

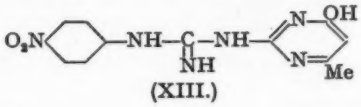
carrying the terminal alkyl group, and we now suggest that it is the contribution of this form to the resonance hybrid that is to be associated with the positive antimalarial activity of these compounds.

The existence of such structural possibilities should be reflected in physical and chemical behaviour, since a conjugated path of the type found therein might be expected to result in the facile transmission of an electronic effect from the anilino-nitrogen (or even from the benzene ring with which this nitrogen atom is also conjugated) to the terminal alkylamino group. This matter is now engaging our attention, but at present it is possible only to give one item of circumstantial evidence in favour of this view. Drug type (X) was prepared (see Part IV, *loc. cit.*) through the corresponding hydroxypyrimidine (XII). This substance

exhibited the properties of a feeble acid, dissolving somewhat in cold dilute sodium hydroxide. The corresponding *p*-nitrophenyl derivative (XIII) appeared to be a stronger acid giving a

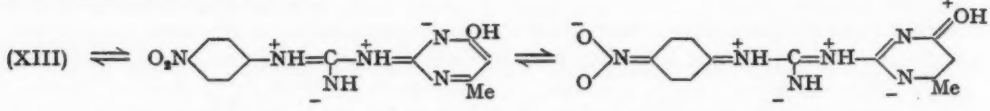


(XII.)

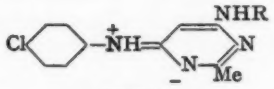


(XIII.)

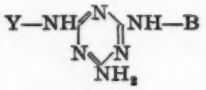
golden-yellow sodium salt. Both colour and increased acidity might be expected if the following processes were facile:



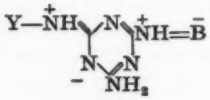
Examination of the inactive pyrimidine type (VIII) shows that the interdependence of the two amidine systems within the molecule (Part VIII, Basford, Curd, and Rose, *J.*, 1946, 713) prevents the formation of a structure exhibiting the therapeutically significant features of the active substances. In this instance a fully conjugated path between the extranuclear atoms cannot be constructed through alternate nitrogen and carbon atoms, but only through C_4, C_5, and C_6 of the pyrimidine ring (XIV). Consideration on the same basis of the 1 : 3 : 5-triazine structures (IV), (V), (VI), and (VII) is difficult at this stage, but here again some



(XIV.)

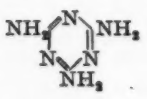


(XV.)

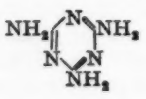


(XVI.)

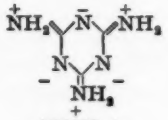
circumstantial evidence is available to suggest how these structures might be expected to behave. Thus, the 1 : 3 : 5-triazine ring is well known in colour chemistry to function as a "chromophoric block", that is to say, a dye molecule of type (XV) in which (Y) and (B) represent the terminal groupings of yellow and blue dye components, respectively, will produce a green shade not dissimilar from that obtained by a physical mixture of the two units. Accepting the current view that the colour of organic dyes is closely connected with resonance (see Pauling, "Gilman's Organic Chemistry", New York, 1943, Chap. 26), this would suggest that asymmetrical structures such as (XVI), whose existence would have to be admitted in



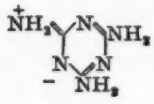
(XVII*a*.)



(XVII*b*.)

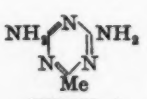


(XVII*c*.)

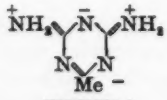


(XVII*d*.)

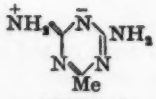
the event of any observed mixing of the chromophoric systems, contribute little to the colour resonance hybrid. Further, Hughes (*J. Amer. Chem. Soc.*, 1941, **63**, 1737), from *X*-ray studies on the crystal structure of melamine, concludes that the three principal structures are (XVII*a*), (XVII*b*), and (XVII*c*), with only minor contributions from the asymmetrical forms such as (XVII*d*). This would accord with the mechanism of the chromophoric block effect suggested in the case of the dye (XV). It might be anticipated therefore that drug structures based on (V) and (VI) would be inactive since the asymmetric disposition of bonds necessary to give an arrangement analogous to that of (IX*d*) in the biologically active pyrimidine series



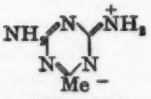
(XVIII*a*.)



(XVIII*b*.)



(XVIII*c*.)

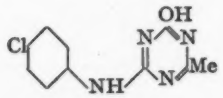


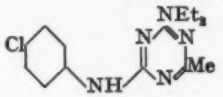
(XVIII*d*.)

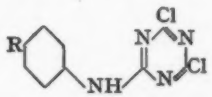
(that is, necessary to provide conjugation through alternate carbon and nitrogen atoms) is unlikely. On the other hand, 2 : 4-diamino-6-methyltriazine (XVIII*a*), of which (IV) is a

derivative, cannot provide a structure analogous to (XVII*c*), the nearest approach being (XVIII*b*). If this asymmetrical arrangement is permissible then there would appear to be less reason for excluding the possible existence of the other asymmetrical forms (XVIII*c*) and (XVIII*d*) which exhibit those structural features tentatively suggested as necessary for antimalarial activity. These points can only be settled with the aid of precise physical data relating to the resonance states of these substances, and until these are available it is not possible to say whether the biological results obtained with the triazine drugs support or invalidate our postulates.

The methods tried for the preparation of the triazine derivatives (IV) were (*a*) acetylation and ring-closure of (III), (*b*) replacement of the hydroxyl group of (XIX), itself obtained from acetic anhydride and *p*-chlorophenyldicyandiamide (compare the preparation of acetoguan-

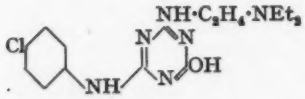

(XIX.)

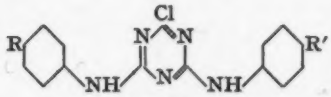

(XX.)

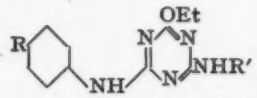

(XXI.)

amine, Andreasch, *Monatsh.*, 1927, **48**, 145) by halogen and subsequent interaction with amines, and (*c*) interaction of (IV; R = H) with amines, *e.g.*, $Et_2N{\cdot}[CH_2]_n{\cdot}NH_2$, with loss of ammonia. The requisite diguanides (III; R = $[CH_2]_2{\cdot}NEt_2$ or $[CH_2]_3{\cdot}NEt_2$) for method (*a*) were described in Part X (*loc. cit.*); by successive treatment with acetic anhydride and alcoholic sodium hydroxide they gave the corresponding triazines (IV). The nature of the initial condensates with acetic anhydride was not investigated since they could not be obtained solid for characterisation, but in a parallel experiment starting with (III; R = H), the product at this stage analysed as (IV; R = Ac) and dissolved in alcoholic sodium hydroxide, presumably as a sodium salt, with the almost immediate deposition of the de-acetylated compound (IV; R = H). The related (XX) was formed analogously from the corresponding N^1-*p*-chlorophenyl-N^5 : N^5-diethyldiguanide. Method (*b*) was successful as far as (XIX), but attempts to replace hydroxyl by chlorine failed. Similarly, no condensation took place by method (*c*) with temperatures up to 170°.

The remaining compounds were obtained starting with cyanuric chloride. The stepwise reaction of this compound with aniline to give (XXI; R = H) has been described by Fierz-David and Matter (*J. Soc. Dyers and Col.*, 1937, **53**, 424). By the same method (XXI; R = Cl) and (XXI; R = OMe) were made. (XXI; R = Cl) reacted with *iso*propylamine, β-diethylaminoethylamine, or α*γ*-bisdiethylamino*iso*propylamine in warm acetone to give {VII; R = Pr^{β}, $[CH_2]_2{\cdot}NEt_2$, or $CH(CH_2{\cdot}NEt_2)_2$}, and interaction of this secondary product at 100° with ammonia gave {V; R = Pr^{β}, $[CH_2]_2{\cdot}NEt_2$, or $CH(CH_2{\cdot}NEt_2)_2$ R′ = H}, and with *p*-chloroaniline gave (VI; R = R′ = Cl; R″ = $[CH_2]_2{\cdot}NEt_2$). In a similar manner (XXI; R = H) and (XXI; R = OMe) reacted successively with β-diethylaminoethylamine and ammonia to give compounds analogous to (VII; R = $[CH_2]_2{\cdot}NEt_2$) and (V; R = $[CH_2]_2{\cdot}NEt_2$, R′ = H). Boiling 2N-hydrochloric acid hydrolysed the secondary product (VII; R = $[CH_2]_2{\cdot}NEt_2$) to (XXII). *p*-Chloroaniline or *p*-anisidine reacted with (XXI; R = Cl or OMe)

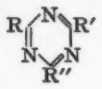

(XXII.)


(XXIII.)


(XXIV.)

in benzene at 80° to give the 2 : 4-diarylamino-6-chloro-1 : 3 : 5-triazine (XXIII; R = R′ = Cl or OMe) and in one experiment some 2 : 4 : 6-triarylamino-1 : 3 : 5-triazine (VI; R = R′ = OMe, R″ = *p*-C_6H_4Cl). With ammonia in ethanol at 120—140° (XXIII; R = R′ = Cl or OMe) gave the melamine derivative (VI; R = R′ = Cl or OMe, R″ = H), but with β-diethylaminoethylamine in ethanol at 120—140° (XXIII; R = R′ = OMe) gave the ethoxy-derivative (XXIV, R = OMe, R′ = *p*-$C_6H_4{\cdot}OMe$). An ethoxy-compound (XXIV; R = Cl, R′ = Pr^{β}) was also obtained when (VII; R = Pr^{β}) reacted similarly with *iso*propylamine.

Compounds Tested for Antimalarial Activity.—Antimalarial activity was determined by the method described by Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139) against *P. gallinaceum* in the chick.

General formula: 

Ref. No.	R.	R′.	R″.	Dose, mg./kg.	Activity.
3492	Cl·C$_6$H$_4$·NH	Et$_2$N·[CH$_2$]$_3$·NH	Me	100	—
3919	,,	Et$_2$N·[CH$_2$]$_3$·NH	,,	80	—
3469	,,	,,	Cl	300	—
3667	,,	,,	NH$_2$	100	—
3689	,,	,,	OH	500	—
5354	,,	,,	Cl·C$_6$H$_4$·NH	120	—
5232	,,	(Et$_2$N·CH$_2$)$_2$CH·NH	Cl	240	—
5237	,,	,,	NH$_2$	120	—
3468	Ph·NH	Et$_2$N·[CH$_2$]$_3$·NH	Cl	200	—
3559	,,	,,	NH$_2$	150	—
3670	MeO·C$_6$H$_4$·NH	,,	Cl	200	—
3343	Cl·C$_6$H$_4$·NH	NH$_2$	Me	200	—
4176	,,	NEt$_2$	,,	400	—
5200	,,	NHPr$^\beta$	Cl	80	—
5228	,,	,,	NH$_2$	120	—
5292	,,	,,	OEt	240	—
3875	,,	Cl·C$_6$H$_4$·NH	NH$_2$	400	—
3874	,,	MeO·C$_6$H$_4$·NH	,,	400	—
3766	,,	,,	MeO·C$_6$H$_4$·NH	400	—
3541	NH$_2$	,,	,,	100	—

Experimental.

2-p-*Chloroanilino*-6-*acetamido*-4-*methyl*-1 : 3 : 5-*triazine* (IV; R = Ac).—*p*-Chlorophenyldiguanide (10 g.) and acetic anhydride (25 c.c.) were heated at 100° for 1 hour. Water (100 c.c.) was added and the solid *product* collected, recrystallised successively from β-ethoxyethanol and glacial acetic acid, washed with ethanol, and dried at 100°, giving 1·7 g., m. p. 269—271° (Found: C, 51·3; H, 4·0; N, 24·7. C$_{12}$H$_{12}$ON$_6$Cl requires C, 51·9; H, 4·3; N, 25·2%).

6-*Amino*-2-p-*chloroanilino*-4-*methyl*-1 : 3 : 5-*triazine* (IV; R = H).—The above acetyl derivative (3·7 g.) was heated with methanol (50 c.c.) and 10N-sodium hydroxide (5 c.c.) added. The initial solution rapidly deposited crystals which were collected and recrystallised from butanol, giving the *base* as colourless needles, m. p. 195—196° (Found: N, 29·2. C$_{10}$H$_{10}$N$_6$Cl requires N, 29·6%). The two stages were conveniently combined for the preparation of larger amounts by warming into solution a mixture of *p*-chlorophenyldiguanide hydrochloride (46 g.), dioxan (100 c.c.), 10N-sodium hydroxide (50 c.c.), and water (50 c.c.) and cautiously stirring in acetic anhydride (40 c.c.). Restoring alkalinity with more sodium hydroxide and adding water (700 c.c.) precipitated 40 g. of a nearly pure product, m. p. 191°.

2-p-*Chloroanilino*-6-β-*diethylaminoethylamino*-4-*methyl*-1 : 3 : 5-*triazine* (IV; R = [CH$_2$]$_2$·NEt$_2$) (3919).—N^1-*p*-Chlorophenyl-N^5-β-diethylaminoethyldiguanide (9 g.) and acetic anhydride (25 c.c.) were refluxed for 1 hour, diluted with water (150 c.c.), and made alkaline with sodium hydroxide. The precipitated oil was washed with water by decantation and boiled for 3 minutes in methanol (90 c.c.) and 10N-sodium hydroxide (9 c.c.). On adding water (150 c.c.) the crude *triazine* crystallised out and after drying gave colourless needles (5·2 g.) from light petroleum (b. p. 100—120°), m.p. 145—146° (Found: C, 57·35; H, 6·7; N, 24·3. C$_{16}$H$_{33}$N$_6$Cl requires C, 57·3; H, 6·9; N, 25·1%).

2-p-*Chloroanilino*-6-γ-*diethylaminopropylamino*-4-*methyl*-1 : 3 : 5-*triazine* (IV; R = [CH]$_3$·NEt$_2$) (3492).—Similarly prepared from N$_1$-*p*-chlorophenyl-N$_5$-γ-diethylaminopropyldiguanide (5 g.) and acetic anhydride (12·5 c.c.), the *triazine* formed colourless crystals from light petroleum (b. p. 100—120°), m. p. 125° (Found: C, 57·8; H, 7·0; N, 23·8. C$_{17}$H$_{25}$N$_6$Cl requires C, 58·5; H, 7·1; N, 24·1%).

2-p-*Chloroanilino*-6-*diethylamino*-4-*methyl*-1 : 3 : 5-*triazine* (XX) (4176).—Similarly prepared from N^1-*p*-chlorophenyl-N^5 : N^5-diethyldiguanide, the *triazine* formed colourless prisms from light petroleum (b. p. 100—120°), m. p. 112° (Found: C, 58·2; H, 6·4; N, 23·6. C$_{14}$H$_{19}$N$_6$Cl requires C, 57·6; H, 6·15; N, 24·0%).

2-p-*Chloroanilino*-4-*hydroxy*-6-*methyl*-1 : 3 : 5-*triazine* (XIX).—*p*-Chlorophenyldicyandiamide (10 g.) and acetic anhydride (20 c.c.) were heated for 10 minutes under reflux and cooled, and the product (3·75 g.) was filtered off and washed with acetic acid. The *triazine* gave crystals from acetic acid, m. p. 341—344° (Found: C, 50·5; H, 4·1; N, 23·5; Cl, 14·3. C$_{10}$H$_9$ON$_4$Cl requires C, 50·7; H, 3·8; N, 23·65; Cl, 15·0%). A *dihydrate*, m. p. 292—294°, was obtained by dissolving in sodium hydroxide solution and precipitating with acetic acid; it crystallised unchanged from dimethylformamide but gave the anhydrous compound, m. p. 340°, when crystallised from acetic acid (Found: C, 44·7; H, 4·1; N, 20·1; Cl, 12·4. C$_{10}$H$_9$ON$_4$Cl,2H$_2$O requires C, 43·9; H, 4·75; N, 20·5; Cl, 13·0%).

2 : 4-*Dichloro*-6-p-*chloroanilino*-1 : 3 : 5-*triazine* (XXI; R = Cl).—Cyanuric chloride (30·75 g.) dissolved in benzene (400 c.c.) was stirred below 10° and *p*-chloroaniline (42·5 g.) dissolved in benzene (250 c.c.) added dropwise. The mixture was stirred for 1 hour at 20°. The precipitated *triazine* was collected, stirred with 2N-hydrochloric acid (250 c.c.), filtered off, and washed with water until free from *p*-chloroaniline hydrochloride. The residual solid (36 g.) melted at 184—186° (evaporation of the benzene mother liquors yielded a further 8·25 g., m. p. 180—184°) and gave colourless needles from benzene, m. p. 185—186° (Found: N, 20·2; Cl, 37·8. C$_9$H$_5$N$_4$Cl requires N, 20·35; Cl, 38·65%).

2 : 4-*Dichloro*-6-p-*anisidino*-1 : 3 : 5-*triazine* (XXI; R = OMe).—Similarly prepared from cyanuric

chloride and *p*-anisidine, the *triazine* formed colourless needles from benzene, m. p. 168—170° (Found : Cl, 25·8. $C_{10}H_8ON_4Cl_2$ requires Cl, 26·2%).

2-*Chloro*-4-*anilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (3468).—2 : 4-Dichloro-6-anilino-1 : 3 : 5-triazine (12·1 g.) in acetone (30 c.c.) was mixed with *β*-diethylaminoethylamine (5·4 g.) in acetone (20 c.c.). After the initial reaction the mixture was boiled under reflux for 30 minutes. The white microcrystalline *hydrochloride* (12·5 g.) was filtered off and washed with acetone; it gave flat microscopic needles from water, m. p. 156° (Found : C, 47·95; H, 6·6; N, 22·0; Cl, 19·0. $C_{15}H_{21}N_6Cl,HCl,H_2O$ requires C, 48·0; H, 6·4; N, 22·4; Cl, 18·95%). The free base gave plates from ethanol, m. p. 150—151°.

2-*Chloro*-4-p-*chloroanilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (VII; R = $[CH_2]_2{\cdot}NEt_2$) (3469).—Prepared from 2 : 4-dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine and *β*-diethylaminoethylamine, the *triazine* gave irregular white platelets from benzene, m. p. 174—175° (Found : N, 23·0; Cl, 18·5. $C_{15}H_{20}N_6Cl_2,H_2O$ requires N, 22·55; Cl, 19·05%). The *hydrochloride* gave colourless prisms from water, m. p. 228° (Found : C, 45·9; H, 5·5; N, 21·3; Cl, 27·0. $C_{15}H_{20}N_6Cl_2,HCl$ requires C, 46·0; H, 5·35; N, 21·45; Cl, 27·2%).

2-*Chloro*-4-p-*anisidino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (3670).—Prepared similarly, this thiazine gave the *hydrochloride* as colourless crystals from water, m. p. 120—121° (Found : C, 46·9; H, 6·5; N, 20·1; Cl, 17·4. $C_{16}H_{23}ON_6Cl,HCl,H_2O$ requires C, 47·3; H, 6·4; N, 20·75; Cl, 17·55%).

2-*Chloro*-4-p-*chloroanilino*-6-*αγ*-*bisdiethylaminoisopropylamino*-1:3:5-*triazine* [VII; R = $CH(CH_2{\cdot}NEt_2)_2$] (5232).—2 : 4-Dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine (7 g.) and *αγ*-bisdiethylamino*iso*propylamine (5 g.) were refluxed with acetone (30 c.c.) for 30 minutes. The *monohydrochloride* separated as a white crystalline powder, m. p. 199—200° (Found : Cl, 21·5; Cl′, 7·0. $C_{20}H_{31}N_7Cl_2,HCl,H_2O$ requires Cl, 21·6; Cl′, 7·2%). The *base* gave white prisms, m. p. 156°, from benzene (Found : N, 22·2; Cl, 15·6. $C_{20}H_{31}N_7Cl_2$ requires N, 22·25; Cl, 16·15%).

2-*Chloro*-4-p-*chloroanilino*-6-iso*propylamino*-1 : 3 : 5-*triazine* (VII; R = Pr^{β}) (5200).—2 : 4-Dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine (14 g.), *iso*propylamine (5 c.c.), and acetone (65 c.c.) refluxed for 30 minutes, filtered from insoluble matter, and diluted with N/2-sodium hydroxide solution (200 c.c.), formed a gum which hardened on rubbing and gave colourless prisms of the *triazine* from benzene, m. p. 164—166° (Found : N, 22·5; Cl, 23·2. $C_{12}H_{13}N_5Cl_2$ requires N, 23·5; Cl, 23·8%).

2-*Amino*-4-*anilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (3559).—2-Chloro-4-anilino-6-*β*-diethylaminoethylamino-1 : 3 : 5-triazine hydrochloride (5 g.) and alcoholic ammonia (40 c.c.) were heated at 120—140° in a sealed tube for 5 hours. Dilution with water (100 c.c.) gave colourless crystals of the *triazine*, m. p. 128—129°, unchanged after crystallisation from benzene (Found : C, 59·0; H, 7·6; N, 32·5. $C_{15}H_{23}N_7$ requires C, 59·7; H, 7·65; N, 32·5%).

2-*Amino*-4-p-*chloroanilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (V; R = H, R′ = $[CH_2]_2{\cdot}NEt_2$) (3667).—Similarly prepared, the *triazine* formed micro-crystals from light petroleum (b. p. 100—120°), m. p. 136—137° (Found : C, 54·0; H, 6·7; N, 28·1. $C_{15}H_{22}N_7Cl$ requires C, 53·6; H, 6·55; N, 29·2%).

2-*Amino*-4-p-*chloroanilino*-6-*αγ*-*bisdiethylaminoisopropylamino*-1 : 3 : 5-*triazine* [V; R = H, R′ = $CH(CH_2{\cdot}NEt_2)_2$] (5237).—Similarly prepared, the *triazine* formed colourless crystals from benzene–ligroin, m. p. 132° (Found : C, 57·3; H, 7·8; N, 26·3. $C_{20}H_{33}N_8Cl$ requires C, 57·0; H, 7·85; N, 26·6%).

2-*Amino*-4-p-*chloroanilino*-6-iso*propylamino*-1 : 3 : 5-*triazine* (V; R = H, R′ = Pr^{β}) (5228).—Similarly prepared, this thiazine gave the *hydrochloride* from water, m. p. 232—234° (Found : N, 25·3; Cl, 21·0. $C_{12}H_{15}N_6Cl,HCl,H_2O$ requires N, 25·2; Cl, 21·35%).

2-p-*Chloroanilino*-4-*β*-*diethylaminoethylamino*-6-*hydroxy*-1 : 3 : 5-*triazine* (XXII) (3689).—2-Chloro-4-*p*-chloroanilino-6-*β*-diethylaminoethylamino-1 : 3 : 5-triazine hydrochloride (5 g.) and 4N-hydrochloric acid (30 c.c.) were refluxed for 4 hours and then filtered. Cooling gave the *dihydrochloride* in needles, m. p. 262—264° (Found : C, 40·2; H, 6·0; N, 19·9; Cl, 23·9. $C_{15}H_{21}ON_6Cl,2HCl,2H_2O$ requires C, 40·3; H, 6·05; N, 18·85; Cl, 23·9%).

2 : 4-*Di*-p-*chloroanilino*-6-*β*-*diethylaminoethylamino*-1 : 3 : 5-*triazine* (VI; R = R′ = Cl, R″ = $[CH_2]_2{\cdot}NEt_2$) (5354).—2-Chloro-4-*p*-chloroanilino-6-*β*-diethylaminoethylamino-1 : 3 : 5-triazine hydrochloride (4 g.), *p*-chloroaniline (1·3 g.), water (20 c.c.), and concentrated hydrochloric acid (0·1 c.c.) were refluxed for 90 minutes. The precipitate of *dihydrochloride* which formed gave colourless crystals from water, m. p. 116—119° (after drying at 100° in vacuum, m. p. 150—154°) (Found : Cl, 26·1; Cl′, 12·7; H_2O, 6·6. $C_{21}H_{25}N_7Cl_2,2HCl,H_2O$ requires Cl, 25·55; Cl′, 12·8; H_2O, 6·5%).

2-*Amino*-4 : 6-*di*-p-*chloroanilino*-1 : 3 : 5-*triazine* (VI; R = R′ = Cl, R″ = H) (3875).—2 : 4-Dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine (10 g.), *p*-chloroaniline (9 g.), and benzene (350 c.c.) were refluxed for 3 hours. The precipitate of 2-*chloro*-4 : 6-*di*-p-*chloroanilino*-1 : 3 : 5-*triazine* (XXIII, R = R′ = Cl) which formed on cooling was lixiviated with dilute hydrochloric acid to remove *p*-chloroaniline. The residue gave colourless prisms from benzene, m. p. 223° (Found : Cl, 27·7. $C_{15}H_{10}N_5Cl_3$ requires Cl, 29·0%). The product (3·7 g.) without further purification, and alcoholic ammonia (25 c.c.) were heated at 120—140° for 3 hours. The precipitate, water washed, dissolved in boiling ethanol (250 c.c.), and treated with charcoal gave on addition of concentrated hydrochloric acid 2-*amino*-4 : 6-*di*-p-*chloroanilino*-1 : 3 : 5-*triazine hydrochloride*, m. p. 276—279° (Found : N, 21·6; Cl, 27·8. $C_{15}H_{12}N_6Cl_2,HCl$ requires N, 21·9; Cl, 27·8%).

2-*Amino*-4 : 6-*di*-p-*anisidino*-1 : 3 : 5-*triazine* (VI; R = R′ = OMe, R″ = H) (3541).—*p*-Anisidine and 2 : 4-dichloro-6-*p*-anisidino-1 : 3 : 5-triazine brought into reaction as above in boiling benzene gave colourless platelets of 2-*chloro*-4 : 6-*di*-p-*anisidino*-1 : 3 : 5-*triazine* (XXIII; R = R′ = OMe) from benzene, m. p. 197—199° (Found : Cl, 9·5. $C_{17}H_{16}O_2N_5Cl$ requires Cl, 9·95%). This, without further purification, reacted with alcoholic ammonia to give a base, m. p. 202—203° from benzene. The *hydrochloride* crystallised from ethanol–hydrochloric acid, m. p. 277° (Found : C, 52·4; H, 5·3; N, 21·1. $C_{17}H_{18}O_2N_6,HCl,H_2O$ requires C, 51·9; H, 5·35; N, 21·4%).

2-*Amino*-4-p-*chloroanilino*-6-p-*anisidino*-1 : 3 : 5-*triazine* (VI; R = Cl, R′ = OMe, R″ = H) (3874).—2 : 4-Dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine (9·2 g.), *p*-anisidine (8·2 g.), and benzene (200 c.c.) were stirred at room temperature for 1·5 hours, then refluxed for 1 hour and filtered hot. 2-*Chloro*-4-p-*chloroanilino*-6-p-*anisidino*-1 : 3 : 5-*triazine* (XXIII; R = Cl, R′ = OMe) crystallised from the filtrate

as colourless prisms, m. p. 186° (Found: Cl, 18·3. $C_{16}H_{19}ON_5Cl_2$ requires Cl, 19·6%). The same substance was obtained from 2 : 4-dichloro-6-*p*-anisidino-1 : 3 : 5-triazine and *p*-chloroaniline. It was used in the next stage without further purification. The material insoluble in hot benzene was lixiviated with dilute hydrochloric acid and the residue of 2-p-*chloroanilino*-4 : 6-*di*-p-*anisidino*-1 : 3 : 5-*triazine hydrochloride* (VI; R = R′ = OMe, R″ = C_6H_4Cl) (3766) gave colourless crystals from acetic acid, m. p. 261° (Found: C, 54·6; H, 4·6; N, 16·7. $C_{33}H_{31}O_2N_8Cl,HCl,H_2O$ requires C, 54·8; H, 4·65; N, 16·7%). 2-Chloro-4-*p*-chloroanilino-6-*p*-anisidino-1 : 3 : 5-triazine and alcoholic ammonia gave 2-amino-4-*p*-chloroanilino-6-*p*-anisidino-1 : 3 : 5-triazine isolated as the *hydrochloride*, m. p. 259—261° (Found: N, 20·3; Cl, 17·65. $C_{16}H_{15}ON_6Cl,HCl,H_2O$ requires N, 20·3; Cl, 17·1%).

2 : 4-*Di*-p-*anisidino*-6-*ethoxy*-1 : 3 : 5-*triazine* (XXIV; R = OMe, R′ = C_6H_4·OMe).—2-Chloro-4 : 6-di-*p*-anisidino-1 : 3 : 5-triazine (3·6 g.), β-diethylaminoethylamine (1·16 g.), and absolute alcohol (30 c.c.) were heated in a sealed tube at 120—140° for 3 hours. The reaction product gave the *hydrochloride*, m. p. 252—253°, from acetic acid–hydrochloric acid (Found: C, 56·1; H, 5·4; N, 16·4; Cl′, 8·4. $C_{19}H_{21}O_2N_5,HCl$ requires C, 56·5; H, 5·45; N, 17·4; Cl′, 8·8%).

2-p-*Chloroanilino*-4-iso*propylamino*-6-*ethoxy*-1 : 3 : 5-*triazine* (XXIV; R = Cl, R′ = Pr^{β}) (5292).—2-Chloro-4-*p*-chloroanilino-6-*iso*propylamino-1 : 3 : 5-triazine (6 g.), absolute alcohol (20 c.c.), and *iso*propylamine (3·5 c.c.) were heated in a sealed tube at 120—140° for 3 hours. The crystalline precipitate, washed with ethanol and water, gave colourless crystals from benzene–light petroleum or aqueous ethanol, m. p. 163—164° (Found: C, 54·6; H, 6·1; Cl, 11·5. $C_{14}H_{18}ON_5Cl$ requires C, 54·55; H, 5·85; Cl, 11·6%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9.

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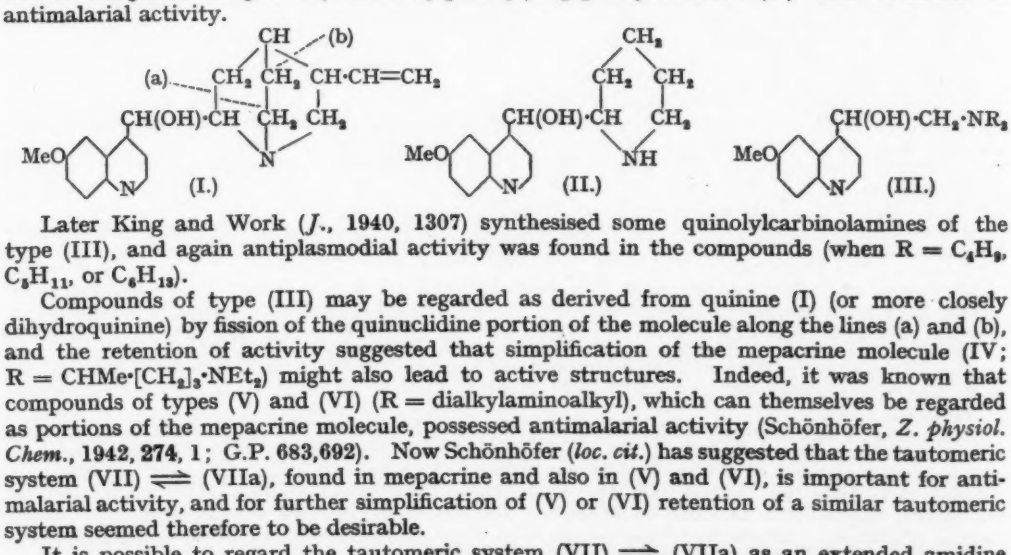
39. *Synthetic Antimalarials. Part XIII. Some N-Dialkylaminoalkylamidines.*

By F. H. S. CURD and C. G. RAISON.

In an attempt to dispense with the heterocyclic structure of mepacrine, series of *N*-β-diethylaminoethylarylamidines and *N*-β-diethylaminoethyl-*N*′-arylarylamidines have been prepared, but none of the compounds exhibited any activity against avian malaria.

THE present investigation was commenced at about the same date as that described in Part I (Curd and Rose, *J.*, 1946, 343), but for various reasons reporting has been delayed. Although none of the compounds now described possesses any antimalarial activity, some of the concepts underlying this investigation have been usefully developed in other directions.

Ainley and King (*Proc. Roy. Soc.*, 1938, *B*, **125**, 60) have shown that the quinine molecule (I) can be simplified to give 4-(6-methoxyquinolyl)-2-piperidylcarbinol (II) with retention of antimalarial activity.



Later King and Work (*J.*, 1940, 1307) synthesised some quinolylcarbinolamines of the type (III), and again antiplasmodial activity was found in the compounds (when R = C_4H_9, C_5H_{11}, or C_6H_{13}).

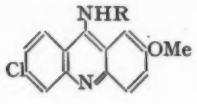
Compounds of type (III) may be regarded as derived from quinine (I) (or more closely dihydroquinine) by fission of the quinuclidine portion of the molecule along the lines (a) and (b), and the retention of activity suggested that simplification of the mepacrine molecule (IV; R = CHMe·$[CH_2]_3$·NEt_2) might also lead to active structures. Indeed, it was known that compounds of types (V) and (VI) (R = dialkylaminoalkyl), which can themselves be regarded as portions of the mepacrine molecule, possessed antimalarial activity (Schönhöfer, *Z. physiol. Chem.*, 1942, **274**, 1; G.P. 683,692). Now Schönhöfer (*loc. cit.*) has suggested that the tautomeric system (VII) ⇌ (VIIa), found in mepacrine and also in (V) and (VI), is important for antimalarial activity, and for further simplification of (V) or (VI) retention of a similar tautomeric system seemed therefore to be desirable.

It is possible to regard the tautomeric system (VII) ⇌ (VIIa) as an extended amidine system RNH–C(=)–CH=CH–N= ⇌ RN=C(–)–CH=CH–NH–, and by the principle of vinylogy (Fuson, *Chem. Reviews*, 1935, **16**, 1) the system RNH–C(=)–N= ⇌ RN=C(–)–NH– is equivalent;

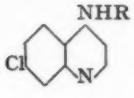
this suggested simplification of (V) to the amidine (VIII; R = Cl, R′ = dialkylaminoalkyl) and of (VI) to (IX; R = dialkylaminoalkyl). Accordingly (IX; R = $[CH_2]_2$·NEt_2) and a series of compounds of type (VIII; R′ = $[CH_2]_2$·NEt_2) with a variety of substituents (R) in the benzene nucleus were prepared.

E.P. 481,814 describes *inter alia* 4-dialkylaminoalkylamino-7 : 8-benzoquinolines (X) and variously substituted derivatives of the same type which by a similar process of modification lead to naphthamidines of the type (XI; R′ = dialkylaminoalkyl); a number of compounds of this type were also prepared. Mention is made in the same patent of azabenzoquinolines (phenanthrolines), and in consequence an aza-derivative (XII) of type (XI) was synthesised.

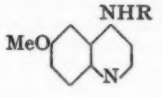
Although none of the compounds of types (VIII), (IX), (XI), and (XII) exhibited any antiplasmodial activity (*P. relictum* and *P. gallinaceum* tests) it was decided to explore a somewhat similar modification of the mepacrine molecule itself, and the preparation of (XIII; R = Cl, R′ = OMe, R″ = CHMe·$[CH_2]_3$·NEt_2) and (XIV) was projected, on the basis of simplifying the extended to a normal amidine system in the two possible ways with retention of either the



(IV.)

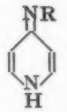


(V.)

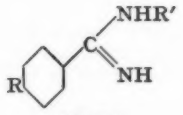


(VI.)

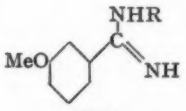
(VII.)



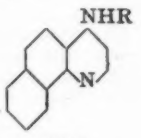
(VIIa.)



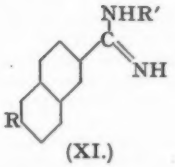
(VIII.)



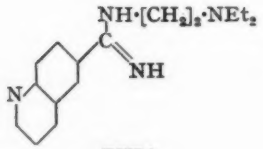
(IX.)



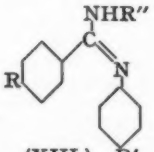
(X.)



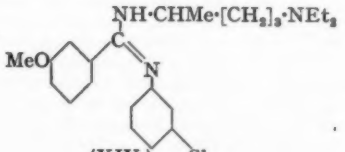
(XI.)



(XII.)



(XIII.) R′



(XIV.) Cl

p-anisidine or the *m*-chloroaniline unit which is the remaining component of the mepacrine molecule. The investigation was, however, abandoned before the synthesis of these actual compounds had been effected; a number of compounds of the same general type such as N′-p-*chlorophenyl*-N-β-*diethylaminoethyl*-p-*methoxybenzamidine* (XIII; R = OMe, R′ = Cl, R″ = $[CH_2]_2$·NEt_2) were however made, but all failed to show any antiplasmodial activity against *P. gallinaceum* in chicks.

The amidines of types (VIII), (IX), (XI), and (XII) were prepared by the well-established method from the corresponding cyanides, which were converted into the iminoethyl-ether hydrochlorides followed by interaction with β-diethylaminoethylamine in alcoholic solution. The synthesis of the related *N*-arylamidines is illustrated by that of N′-p-*chlorophenyl*-N-β-*diethylaminoethylbenzamidine* (XIII; R = H, R′ = Cl, R″ = $[CH_2]_2$·NEt_2) which was obtained from benz-*p*-chloroanilide by conversion, with phosphorus pentachloride, into the iminochloride, and interaction of this with β-diethylaminoethylamine.

Experimental.

m-*Methoxyphenyl Cyanide*.—This has been prepared previously from *m*-methoxybenzamide by Bailar (*J. Amer. Chem. Soc.*, 1930, **52**, 3596), but he gave no experimental details.

m-Methoxybenzaldehyde (Posner, *J. pr. Chem.*, 1910, **82**, 431) (73 g.) was stirred with alcohol (125 c.c.), and a solution of sodium hydroxide (26·8 g.) in water (60 c.c.) added followed by hydroxylamine sulphate (55·3 g.). The temperature rose to 60°, was maintained at 60—70° for ½ hour, and the mixture then left to cool overnight. It was diluted with water (1·5 l.) and acidified with acetic acid, and the oxime extracted with ether. Removal of the ether from the dried extract left an oil (63 g.) which was refluxed for 5 hours, with stirring, with a mixture of acetic anhydride (570 c.c.) and fused sodium acetate (93 g.), and then poured into water (1·25 l.). When the acetic anhydride had decomposed the liquid was cooled, treated with anhydrous sodium carbonate (500 g.), and extracted with ether. The extract, after being washed with sodium carbonate solution and water and dried, was evaporated to yield the cyanide as a

colourless liquid, b. p. 116—120°/13 mm. (yield, 45 g.) (Found: C, 71·7; H, 5·2. Calc. for C_8H_7ON: C, 72·2; H, 5·3%).

2-Cyano-6-methoxynaphthalene.—A mixture of 2-bromo-6-methoxynaphthalene (Franzen and Stäuble, *J. pr. Chem.*, 1922, **103**, 352) (25 g.), cuprous cyanide (10·7 g.), and pyridine (9·3 g.) was heated at 180—190° for 15 hours. The reaction mixture was dissolved in hot pyridine (70 c.c.) and the solution poured into ammonia (*d* 0·088, 145 c.c.) and water (435 c.c.) with stirring. The resulting suspension was well shaken with ether and, after filtration, the ether was washed with dilute hydrochloric acid, then with water, dried, and evaporated. Crystallisation of the residue from light petroleum (charcoal) yielded the *compound* as colourless needles, m. p. 104—106° (yield, 67%) (Found: C, 78·2; H, 4·7; N, 7·6. $C_{12}H_9ON$ requires C, 78·7; H, 4·9; N, 7·65%).

6-Hydroxy-2-cyanonaphthalene.—Attempts to prepare this by a Sandmeyer reaction on 6-amino-2-naphthol were not very successful, the best yield obtained being 13%. The reaction between 6-bromo-2-naphthol and cuprous cyanide in the presence of pyridine was unpromising. This may have been due to a reaction involving the phenolic group, since when this was acetylated a cyanide was readily obtained.

6-Bromo-2-acetoxynaphthalene (m. p. 110—111°; lit. m. p. 103°) (107 g.), cuprous cyanide (41·4 g.), pyridine (35·9 g.), and a trace of anhydrous copper sulphate (cf. Koelsch and Whitney, *J. Org. Chem.*, 1941, **6**, 795) were heated with stirring at 180—190° for 8 hours. The mixture was then dissolved in hot pyridine (220 c.c.), added to a stirred solution of sodium cyanide (150 g.) in water (1·5 l.), and the mixture extracted with ether. The extract, after being washed with dilute hydrochloric acid and water, was dried (Na_2SO_4) and evaporated to leave a solid (62 g.), m. p. *ca.* 110—120°, which appeared to be a mixture of 2-cyano-6-acetoxynaphthalene and the required cyanonaphthol. It was added to a stirred and cooled solution of potassium hydroxide (36 g.) in methanol (220 c.c.); it dissolved rapidly and in a short time a crystalline precipitate began to separate. After being stirred for 1 hour the mixture was diluted with water to 1 l., and the solution clarified by ether extraction and then acidified with hydrochloric acid. The precipitate, washed and dried in ether solution followed by evaporation of the solvent, was crystallised from aqueous alcohol to yield the *cyanonaphthol* (yield, 62%), m. p. 164—166°. It separated from benzene in colourless prisms, m. p. 166—167° (Found: C, 78·1; H, 3·9; N, 8·2. $C_{11}H_7ON$ requires C, 78·1; H, 4·1; N, 8·2%).

When the crude substance, m. p. 110—120°, was crystallised, first from aqueous methanol and then several times from benzene–petrol, pure *2-cyano-6-acetoxynaphthalene* was obtained (yield, ca 33%) as colourless plates, m. p. 102—103° (Found: C, 74·2; H, 4·2; N, 6·6. $C_{13}H_9O_2N$ requires C, 73·9; H, 4·3; N, 6·6%).

6-Bromo-2-cyanonaphthalene.—Ice water (250 c.c.), surrounded by an ice and salt mixture, was stirred whilst hydrochloric acid (70 c.c.) followed by an aqueous solution of sodium nitrite (7·5 g.) was added. A cold solution of 6-bromo-2-naphthylamine (22·2 g.) in acetic acid (120 c.c.) was then added in a rapid thin stream with vigorous stirring. The acidity of the diazonium solution to Congo red was removed by the addition of sodium acetate, and the solution was then run into a stirred solution of cuprous cyanide in sodium cyanide [from copper sulphate (50 g.)] at 70—80°. After cooling, the product was filtered off and digested with a mixture of equal parts of concentrated hydrochloric acid and water, washed, dried, and extracted with boiling alcohol (500 c.c.). The filtered extract was evaporated and the residue crystallised from benzene–methanol and then from alcohol to give the *compound* (yield, 22%) as stout orange needles, m. p. 160—162° (Found: C, 56·6; H, 3·2; N, 6·1. $C_{11}H_6NBr$ requires C, 56·9; H, 2·6; N, 6·0%).

The other cyano-compounds used were made by literature methods.

Preparation of Imino-ether Hydrochlorides.—A solution or suspension of the cyano-compound (1 mol.) in dry chloroform containing absolute alcohol (3—4 mols.) was saturated at 0° with hydrogen chloride and left at room temperature for a few days. After evaporation to dryness under reduced pressure at 30°, the last traces of hydrogen chloride were removed in a desiccator. The yields were approximately quantitative. With the exception of *p*-acetamidobenzimino-ether hydrochloride which was extremely hygroscopic, the imino-ether hydrochlorides were colourless solids stable at room temperature and were not subjected to any further treatment before use. 6-Methoxy-2-naphthimino-ether formed a *dihydrochloride* (Found: Cl, 23·7. $C_{14}H_{15}O_2N,2HCl$ requires Cl, 23·5%).

N-β-Diethylaminoethylamidines.—The compounds listed in Table I were prepared by stirring the appropriate imino-ether hydrochloride (1 mol.) with 8—10 times its weight of absolute alcohol containing β-diethylaminoethylamine (1·05 mols.) for 8 hours at 40—45°. The alcohol was then removed under reduced pressure at 30° and the residue treated with water and sufficient hydrochloric acid to make the solution acid to Congo-red. After being warmed for a short time the solution was cooled, and any non-basic material removed by filtration or extraction with ether. The acid solution was then evaporated under reduced pressure at 40°, the last traces of water being removed by repeated evaporation with benzene–alcohol. In cases where the hydrochloride failed to crystallise conversion to either the hydrobromide or the nitrate gave a crystalline salt. After *p*-acetamidobenziminoether hydrochloride had been condensed with β-diethylaminoethylamine in the above manner and the alcohol removed, the residue was deacetylated by boiling with 7% hydrochloric acid for 3 hours. The yield of amidine was usually 75—80%.

Iminochlorides.—The iminochlorides from benz-*p*-chloro-, -*p*-methoxy-, -*m*-chloro-, and -3:5-dichloroanilides were made according to Chapman (*J.*, 1927, 1743; 1932, 1770); those from 2:4-dichlorobenz-*p*-anisidide (m. p. 40—42°) and *p*-methoxybenz-*p*-chloroanilide (m. p. 90—92°), which appear to be new compounds, were prepared in the same way but were not analysed.

N'-Aryl-N-β-diethylaminoethylamidines.—The appropriate iminochloride (1 mol.) was added to a solution of β-diethylaminoethylamine (1 mol.) in 12 times its weight of alcohol cooled to − 10°, and after being stirred below 0° for 3 hours the mixture was warmed slowly to 40—45° and maintained at this temperature for 8 hours. The alcohol was then removed under reduced pressure at 30°, and the residue treated with aqueous sodium hydroxide and extracted with ether. The ether extract was shaken with 5% acetic acid, the acid extract rendered alkaline with sodium hydroxide, and the liberated amidine again extracted with ether. Evaporation of the dried (K_2CO_3) ether extract left the amidine

TABLE I.

N-Diethylaminoethylamidines, $CHR(:NH)\cdot NH\cdot CH_2\cdot CH_2\cdot NEt_2$.

TABLE I.

N-*Diethylaminoethylamidines*, $CHR(:NH)\cdot NH\cdot CH_2\cdot CH_2\cdot NEt_2$.

Ref. No.	Nature of R.	Formula.	M. p.	Analysis. Found (%). C.	H.	Cl.	Required (%). C.	H.	Cl.
2563	*p*-Anisyl	$C_{14}H_{23}ON_3,2HCl$ (EtOH–EtOAc)	214—216° (decomp.)	52·9	8·05	22·2	52·2	7·8	22·05
2564	*m*-Anisyl	$C_{14}H_{23}ON_3,2HBr$ (EtOH–EtOAc)	180—181 (decomp.)	40·5	5·9	38·5 (Br)	40·9	6·1	38·9 (Br)
2565	*p*-Chlorophenyl	$C_{13}H_{20}N_2Cl,2HCl,H_2O$ (EtOH–EtOAc)	244—246 (decomp.)	45·1	6·9	31·4	45·3	6·9	30·9
2566	6-Methoxy-2-naphthyl	$C_{18}H_{25}ON_3,2HCl$ (EtOH)	221—223 (decomp.)	58·2	7·3	19·1	58·1	7·3	19·1
2567	Phenyl	$C_{13}H_{21}N_3,2HBr$ (EtOH)	234—235 (decomp.)	41·2	5·75	41·2 (Br)	41·0	6·0	42·0 (Br)
2568	6-Hydroxy-2-naphthyl	$C_{17}H_{23}ON_3,2HCl,\frac{1}{2}H_2O$ (EtOH)	257—259 (decomp.)	55·4	7·4	18·9	55·6	7·1	19·3
2586	*p*-Hydroxyphenyl	$C_{13}H_{21}ON_3,2HNO_3$ (EtOH–EtOAc)	148—150 (decomp.) after sintering at 130—135	43·8	6·8	19·2 (N)	43·2	6·4	19·4 (N)
2622	2-Naphthyl	$C_{17}H_{23}N_3,2HBr$ (EtOH)	228—230 (decomp.)	47·0	6·3	36·4 (Br)	47·3	5·8	37·1 (Br)
2634	*p*-Aminophenyl	$C_{13}H_{22}N_4,3HCl$ ($EtOH–H_2O–COMe_2$)	Decomp. 284	46·1	7·5	30·5	45·4	7·3	31·0
2636	6-Quinolyl	$C_{16}H_{22}N_4,3HBr$ (MeOH–EtOAc)	259—261 (decomp.)	37·2	5·0	46·0 (Br)	37·4	4·9	46·8 (Br)
2766	6-Bromo-2-naphthyl	$C_{17}H_{22}N_3Br,2HCl$ (MeOH–EtOAc)	Indef. 235—250, then decomp.	48·3	5·7	1 mg. ≡ 1·14 mg. AgX	48·5	5·7	1 mg. ≡ 1·13 mg. AgX

TABLE II.

N′-*Aryl*-N-*diethylaminoethylamidines*, $CR(:NR')\cdot NH\cdot CH_2\cdot CH_2\cdot NEt_2$.

Ref. No.	R.	R′.	Formula.	M. p	Analysis. Found (%). C.	H.		Required (%). C.	H.	
2660	Phenyl	*p*-Chlorophenyl	$C_{19}H_{24}N_3Cl,2HNO_3$ (EtOH)	Decomp. 154°	50·0	5·65	15·05 (N)	50·05	5·7	15·4 (N)
3175	,,	*p*-Anisyl	$C_{20}H_{27}ON_3,2HI$ (EtOH)	181—183	41·15	5·2	43·0 (I)	41·3	5·0	43·7 (I)
3176	,,	3 : 5-Dichlorophenyl	$C_{19}H_{23}N_3Cl_2,2HNO_3$ (EtOH–EtOAc)	Decomp. 147	46·5	5·1	14·5 (Cl)	46·5	5·1	14·5 (Cl)
3177	,,	*m*-Chlorophenyl	$C_{19}H_{24}N_3Cl,2HI$ (EtOH)	114—116 (decomp.)	39·5	4·3	1 mg. ≡ 0·976 mg. AgX	39·0	4·4	1 mg. ≡ 1·047 mg. AgX
3178	2 : 4-Dichlorophenyl	*p*-Anisyl	$C_{20}H_{25}ON_3Cl_2,2HI$ (EtOH–EtOAc)	237—238 (decomp.)	37·0	4·25	1 mg. ≡ 1·145 mg. AgX	36·9	4·15	1 mg. ≡ 1·165 mg. AgX
4536	*p*-Anisyl	*p*-Chlorophenyl	$C_{20}H_{26}ON_3Cl,2HI$ (EtOH)	Decomp. >150	38·9	4·85	1 mg. ≡ 0·845 mg. AgX	39·0	4·6	1 mg. ≡ 0·996 mg. AgX

base as an oil. The hydriodide or nitrate proved to be the easiest salts to crystallise. The base was converted into the salt by dissolving it in dilute acid to give a solution faintly acid to Congo-red followed by evaporation under reduced pressure, finally with the addition of alcohol–benzene. The average yield of amidine, calculated on the iminochloride, was 56%. The compounds prepared are listed in Table II.

IMPERIAL CHEMICAL INDUSTRIES LTD., RESEARCH LABORATORIES,
BLACKLEY, MANCHESTER, 9.

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40. *Synthetic Mydriatics. Diphenylchloroacetyl Chloride as a Reagent for the Preparation of Benzilic Esters of Tertiary Amino-alcohols.*

By F. E. KING and D. HOLMES.

The benzilic esters of β-dimethylaminoethanol, 4-diethylaminobutan-2-ol, *trans*-2-dimethyl- and -diethyl-amino*cyclo*hexanol and phenyl-β-dimethylaminoethylcarbinol, mostly in the form of their simple quaternary salts, have been prepared for evaluation as mydriatics. A convenient synthesis has been developed in which the tertiary amino-alcohols, or their hydrochlorides or metho-chlorides, are esterified with diphenylchloroacetyl chloride, the resulting chloro-esters being converted into the corresponding esters of benzilic acid by heating with water.

VARIOUS benzilic esters of amino-alcohols have from time to time been the subject of pharmacological investigations, and the recent work of Blicke and Maxwell (*J. Amer. Chem. Soc.*, 1942, **64**, 428; 1943, **65**, 1967) and of Ford-Moore and Ing (this vol., p. 55) has shown that certain quaternary salts of the simple dialkylaminoethyl benzilates possess mydriatic properties comparable with those of atropine. Extending these synthetical experiments to other benzilic esters, for example, those of secondary and/or cyclic alcohols—which consequently have rather more in common with the natural base—a new method for the preparation of benzilic esters has been elaborated.

Hitherto, the mydriatic benzilates have been obtained either by the action of salts of the basically substituted halides on potassium benzilate, or by heating the free aminoalkyl halides with benzilic acid in an organic solvent (Horenstein and Pählicke, *Ber.*, 1938, **71**, 1645; Blicke and Maxwell, *loc. cit.*). The preparation of the necessary halides is, however, sometimes inconvenient, and experiments were undertaken to synthesise the required esters by the method generally used for tropeines, *viz.*, the action of the acetylated hydroxy-acid chloride on the amino-alcohol, followed by hydrolysis of the protecting acetyl group.

Acetylbenzilic acid was obtained by acetylation with acetic anhydride at 100°, as described by La Mer and Greenspan (*J. Amer. Chem. Soc.*, 1934, **56**, 956), who showed that the recrystallised derivative is a monohydrate requiring prolonged vacuum desiccation over sulphuric acid for complete dehydration. Our attempts to hasten the removal of water by heating, etc., gave uncrystallisable products, but shaking in ether solution with anhydrous copper sulphate gave the dehydrated acid in two or three days. Hurd and Williams (*ibid.*, 1936, **58**, 967) claim that the action of boiling thionyl chloride on the anhydrous acid gives acetylbenzilyl chloride in 48% yield, but they have not recorded an analysis for their product, and, despite many attempts under various conditions, we have failed to obtain a homogenous specimen of the desired compound.

While searching for some more stable substituted benzilic acid for use during the acid chloride stage, the labile character of the halogen atom in diphenylchloroacetic acid and its derivatives was noted (cf. Bickel, *Ber.*, 1889, **22**, 1538). The chloro-acid chloride is readily obtained from benzilic acid in one operation, and so the synthesis indicated by the following equation was investigated:

$$CPh_2Cl{\cdot}COCl + H{\cdot}OR \longrightarrow CPh_2Cl{\cdot}CO_2R \longrightarrow CPh_2(OH){\cdot}CO_2R$$

Later, a reference to the use of this method for the synthesis of benzilyl-ψ-tropine was encountered (Wolfes and Hromatka, D.R.-P. 655,404; *Chem. Centr.*, 1938, I, 2755), but no practical details are to be found in available sources.

The basic alcohol chosen for the first experiments was choline, since benzilylcholine chloride (β-dimethylaminoethyl benzilate methochloride) was already known from the work of Ford-Moore and Ing (*loc. cit.*). Starting from β-aminoethanol, which was methylated by the formic acid–paraformaldehyde method (cf. *J.*, 1945, 278), choline chloride was prepared from the resulting dimethylaminoethanol by converting it into the methiodide, which was then treated with silver chloride. The product obtained by heating the dry metho-salt with diphenylchloro-

acetyl chloride—presumably the diphenylchloroacetylcholine chloride—gave β-dimethylaminoethyl benzilate methochloride on dissolving in boiling water. The process was then applied to the readily prepared 4-diethylaminobutan-2-ol, a reduction product of the corresponding Mannich ketone, and it was shown that the identical *diphenylchloroacetate hydrochloride* was obtainable from either the free diethylaminobutanol or its hydrochloride. Hydrolysis with boiling water and neutralisation gave the crystalline 4-*diethylamino*-2-*butyl benzilate*. The amine methiodide on double decomposition with silver chloride gave the benzilate *methochloride*, which proved to have only about 6% of the mydriatic activity of atropine.

In view of the presence in tropine of a cyclic secondary alcohol group, new syntheses were undertaken with amino-*cyclo*hexanols. 2-Amino-*cyclo*hexanols are obtainable from *cyclo*hexene oxide, which reacts with simple amines to give products of *trans*-configuration (cf. Godchot and Mousseron, *Compt. rend.*, 1932, **194**, 981). *trans*-2-Dimethylamino*cyclo*hexanol, formed when dimethylamine is used (Kötz and Merkel, *J. pr. Chem.*, 1926, **113**, 63), gave on heating with diphenylchloroacetyl chloride the expected *chloro-ester hydrochloride*, and this was hydrolysed to the *benzilate hydrochloride* by dissolving in boiling water. The free base combined without difficulty with methyl iodide, and the *methiodide* and corresponding *methochloride* were readily crystallised. On the other hand, formation of the *ethiodide*, from which an *ethochloride* was prepared, was appreciably slower. An attempt to condense trans-2-*dimethylamino*cyclo*hexanol methochloride* with diphenylchloroacetyl chloride, as an alternative route to the foregoing benzilate methochloride, was unsuccessful.

Homologues in the 2-diethylamino*cyclo*hexanol series have also been synthesised, the *trans*-diethylamino*cyclo*hexanol (Brunel, *Ann. Chim. Phys.*, 1905, **6**, 259) reacting readily with the chloro-acid chloride at 100—105°. The resulting 2-*diethylamino*cyclo*hexyl diphenylchloroacetate hydrochloride* was rapidly hydrolysed to the *benzilate hydrochloride* by boiling water. Heating with methyl iodide in a sealed tube was necessary to obtain the methiodide, which was converted into the *benzilate methochloride* in the usual way. The diethylamino-ester failed to react with ethyl iodide, except under conditions which led to decomposition.

The mydriatic properties of ephedrine, adrenaline, and similar amino-alcohols likewise encouraged investigations on the benzilic esters of this series. Phenyl-β-dimethylaminoethylcarbinol, which can readily be prepared from the corresponding ketone (Mannich and Heilner, *Ber.*, 1922, **55**, 359), is a homologue of the ephedrine type, and the preparation of its benzilate was therefore attempted. The action of diphenylchloroacetyl chloride on the free base failed, however, to give a crystalline product, and when the amine hydrochloride was substituted, dehydration ensued giving γ-phenylallyldimethylamine, isolated as *hydrochloride*. The identity of the unsaturated base was proved by reduction to γ-phenylpropyldimethylamine, which was characterised by the melting points of its known salts. Nevertheless, the properties of the unsaturated hydrochloride are not in agreement with those already recorded by Mannich and Chang (*ibid.*, 1933, **66**, 419) for the apparently identical salt, and it is probable that the two compounds are *cis–trans*-isomerides.

In the meantime, further experiments with 2-diethylamino*cyclo*hexanol had shown that, on mixing diphenylchloroacetyl chloride with *twice* the theoretical quantity of amino-alcohol in an inert solvent, ester formation occurs in the cold, the second molecule of the base precipitating as hydrochloride. The application of this technique to phenyl-β-dimethylaminoethylcarbinol resulted in the formation of a high yield of the chloro-ester, hydrolysed by boiling water to the required *benzilate*, from which was obtained the crystalline *methochloride*.

Finally, a lower homologue of the foregoing amino-alcohol, *i.e.*, phenyldimethylaminomethylcarbinol, was prepared, and characterised by its crystalline *hydrochloride* and *methiodide*.

The specific character of the β-aminoethanol grouping in conferring mydriatic properties in the series of benzilic esters is emphasised by tests, kindly carried out by Professor J. H. Burn, F.R.S., and Miss E. Bülbring, Department of Pharmacology, Oxford, which revealed that none of the new benzilic esters described in this paper possesses more than very slight mydriatic activity.

Experimental.

Acetylbenzilic Acid (cf. La Mer and Greenspan, *loc. cit.*).—A solution of benzilic acid (50 g.) in acetic anhydride (100 c.c.) was heated for 10 hours on a steam-bath, cooled, and as much water added as possible without causing turbidity (*ca.* 25 c.c.). Within 2 or 3 hours the crystalline acetate had begun to separate, and from then on further small quantities of water were added at intervals to a total of *ca.* 200 c.c. The resulting acetylbenzilic acid monohydrate (51—55 g.) had m. p. 96—97°. Dissolution in alcohol (150 c.c.) at 40° (charcoal) and precipitation with water (200 c.c.) gave the pure acetyl compound (42 g., 68%), m. p. 97°. Acetylation in presence of sulphuric acid (5 g./100 c.c. acetic anhydride) or sodium acetate (12—13 g./100 c.c.) effected no significant improvement in yield.

In attempting to prepare the anhydrous acetyl derivative, benzilic acid was treated with acetyl chloride as in the preparation of acetylmandelic acid (*Org. Synth.*, IV, 1). It was necessary to heat the mixture to dissolve the acid, and evaporation left an uncrystallisable syrup. When the mixture of acid and acetyl chloride was left overnight at room temperature, large colourless tablets were formed, m. p. 117—118° after crystallisation from benzene–petroleum, which were probably diphenylchloroacetic acid.

La Mer and Greenspan obtained the anhydrous acetylated acid by 3 weeks' desiccation at room temperature. In trying to shorten the time of drying, a specimen of the acid monohydrate was heated at 50—55°/15 mm. in presence of phosphoric anhydride for 2 hours. A colourless sticky glass had then formed, and the odour of acetic acid was detected. Evaporation of a solution of the hydrate (4 g.) in anhydrous benzene (100 c.c.) at 35°/16 mm. also gave a non-crystalline product. The recrystallised hydrate (20 g.) was therefore dissolved in dry ether (200 c.c.) to which anhydrous copper sulphate (20 g.) was added. After being shaken at intervals for 2—3 days, the solution was filtered and evaporated below 25° under reduced pressure, and the anhydrous acid (15·5 g.), m. p. *ca.* 103°, obtained by trituration with light petroleum.

Following Hurd and Williams (*loc. cit.*), the anhydrous acid was heated for 2 hours with purified thionyl chloride. Distillation at 15 mm. was accompanied by considerable decomposition and gave a reddish-yellow product (30—35% yield), but, as recorded by the American authors, it afforded a crystalline anilide. An ether solution (200 c.c.) of the anhydrous acid (8·6 g.) and thionyl chloride (2½ mol.) which 2½ hours later was gently refluxed for 30 minutes, gave on distillation at 0·5 mm. (air-bath at 155°) a pale yellow oil (2·9 g.), but analysis showed it to be impure. Similarly, experiments in which both hydrated and anhydrous acetylbenzilic acid were left with thionyl chloride for various times (up to 15 hours) at room temperature, the surplus reagent then being removed under reduced pressure, also failed to give a homogeneous product.

Diphenylchloroacetyl Chloride (cf. Bickel, *loc. cit.*; Billman and Hidy, *J. Amer. Chem. Soc.*, 1943, **65**, 760).—When the energetic reaction between phosphorus pentachloride (38 g., 2·08 mols.) and benzilic acid (20 g., 1 mol.) had subsided, the mixture was heated at 100° for 15 minutes. Phosphoryl chloride was then removed under diminished pressure at 60—70°, and the residue shaken with ice and water. The solid product was taken up in light petroleum (b. p. 45—55°), dried (Na_2SO_4), the solution evaporated and diphenylchloroacetyl chloride obtained as a colourless solid, m. p. 50—51°, b. p. 139—143°/0·15—0·2 mm., yield 75%.

β-Dimethylaminoethanol.—Ethanolamine (30·5 g., 1 mol.) was neutralised with anhydrous formic acid (46 g., 2 mol.) and the solution cautiously heated with paraformaldehyde (30 g., 2 mol.). At *ca.* 100° a vigorous evolution of carbon dioxide occurred, after which the dark red liquid was heated at 130—140° for 30 minutes. Distillation gave a colourless aqueous solution (45 g.), b. p. 100—135°/748 mm., of β-dimethylaminoethanol identified by the picrolonate, which separated from alcohol in long yellow needles, m. p. 195—197° (Knorr and Matthes, *Ber.*, 1901, **34**, 3484, give m. p. 197°) (Found: C, 47·9; H, 5·6. Calc. for $C_4H_{11}ON,C_{10}H_8O_8N_4$: C, 47·6; H, 5·4%). The aqueous base (44·5 g.) was dissolved in methyl alcohol (30 c.c.) and treated with methyl iodide (70 g.). After refluxing for 30 minutes the solution was evaporated and the crystalline residue (77 g., indicating a 67% yield in the ethanolamine methylation) was recrystallised from methyl alcohol. Choline iodide was thus obtained in shining deliquescent plates, m. p. *ca.* 262—264° (efferv.). The chloride obtained therefrom by treating it in aqueous methyl alcohol with silver chloride, crystallised from acetone containing a little alcohol in deliquescent needles, m. p. >300°.

β-Dimethylaminoethyl Benzilate Methochloride.—A mixture of diphenylchloroacetyl chloride (2·6 g., 1 mol.) and choline chloride (1·4 g., 1 mol.) was heated for 1 hour in an oil-bath at 110°, hydrogen chloride being evolved. The product, a clear glassy solid, failed to crystallise and it was therefore dissolved in boiling water (18—20 c.c.). Next day, the voluminous crystalline mass (2·8 g.) which had formed was crystallised from ethyl acetate containing a little methyl alcohol. The methochloride separated in sheaves of minute prisms, m. p. 216° (efferv.) [Ing records m. p. 216° (decomp.)] (Found: C, 65·1; H, 6·8. Calc. for $C_{18}H_{21}O_3N,CH_3Cl$: C, 65·2; H, 6·9%).

4-Diethylamino-2-butyl Diphenylchloroacetate Hydrochloride.—(*a*) A mixture of 4-diethylamino-butan-2-ol hydrochloride (2·2 g.) and diphenylchloroacetyl chloride (3·75 g.) when heated at 100° for 50 minutes evolved hydrogen chloride. The resulting clear amber syrup was dissolved in acetone, and the *hydrochloride* crystallised on standing in colourless, stout rectangular prisms (3 g.), m. p. 120° (Found: C, 64·3; H, 6·9. $C_{22}H_{29}O_2NCl,HCl$ requires C, 64·4; H, 7·1%).

(*b*) Using the free amino-alcohol (1·8 g.), which reacted exothermally with the acid chloride (3·9 g.), a clear syrup was formed which solidified during heating at 100° for 30 minutes. By treatment with acetone the identical hydrochloride (5 g.) (m. p. and mixed m. p.) was obtained, the higher yield being due to more economical crystallisation.

4-Diethylamino-2-butyl Benzilate.—The foregoing diphenylchloroacetate hydrochloride (5 g.), which is sparingly soluble in cold water, was heated on a steam-bath with water (40 c.c.) for 4 minutes. Next day, the clear solution was evaporated to dryness under diminished pressure, but the residue could not be crystallised, and it was therefore redissolved and the solution neutralised with aqueous sodium hydroxide. The liberated hydroxy-ester was removed in ether which was dried and evaporated, leaving a gum that later solidified. The *benzilate* separated from a small quantity of light petroleum in thick prisms, m. p. 44° (Found: C, 74·4; H, 8·2. $C_{22}H_{29}O_3N$ requires C, 74·4; H, 8·2%). When dissolved in alcoholic picrolonic acid a deep yellow *picrolonate*, m. p. 141°, was obtained (Found: C, 61·7; H, 6·0. $C_{22}H_{29}O_3N,C_{10}H_8O_8N_4$ requires C, 62·0; H, 6·0%).

4-Diethylamino-2-butyl Benzilate Methochloride.—The addition of methyl iodide (3 g.) to a dry ether solution of the benzilic ester (3 g.) soon gave a flocculent amorphous precipitate. This could not be crystallised, but was disssolved next day in water (40 c.c.) and methyl alcohol (20 c.c.), shaken with freshly precipitated silver chloride (3 g.), and heated on a steam-bath before filtration. Evaporation under diminished pressure gave a clear gum which crystallised in contact with acetone, in which the *methochloride* is very sparingly soluble. By precipitation from a very small volume of ethyl alcohol with

hot ethyl acetate the pure salt was obtained in spheroidal aggregates of prisms, m. p. after drying in a vacuum, 173—175° (Found: C, 67·7; H, 7·5. $C_{22}H_{29}O_3N,CH_3Cl$ requires C, 68·1; H, 7·9%).

trans-2-*Dimethylamino*cyclo*hexanol*.—The preparation of the dimethylamino*cyclo*hexanol from *cyclo*hexene (*Org. Synth.*, V, 31) followed closely the method of Kötz and Merkel (*loc. cit.*). The product, b. p. 83—83·5°/13 mm., was obtained in 93% yield, and gave a *picrate* crystallising from ethanol in fine pale yellow needles, m. p. 149—150° (Found: C, 45·4; H, 5·4. $C_8H_{17}ON,C_6H_3O_7N_3$ requires C, 45·2; H, 5·4%). The amine methodide separated from alcohol–ethyl acetate in stout rods, m. p. 217—217·5° (Wilson and Read, *J.*, 1935, 1273, record m. p. 214°), and the *methochloride* in colourless deliquescent needles, m. p. 253—254° (decomp.), from ethyl acetate containing ethanol. An attempt to convert this compound into a diphenylchloroacetate did not succeed, apparently owing to the insolubility of the metho-salt in the fused acid chloride.

2-*Dimethylamino*cyclo*hexyl Diphenylchloroacetate Hydrochloride*.—When molten diphenylchloroacetyl chloride (10 g.), supercooled to 40°, was added with stirring to 2-dimethylamino*cyclo*hexanol (5 g.), an exothermic reaction occurred accompanied by slight charring. The pasty mass, frequently stirred, was heated at 105—110° for 2¼ hours and afterwards refluxed with dry acetone (10 c.c.). When cold, the product was collected and washed with acetone which left the *diphenylchloroacetate hydrochloride* as a colourless solid (10·8 g., 76%), m. p. 178—185°. A sample recrystallised from dry acetone–methyl alcohol by precipitation with ether separated in spherical aggregates of small plates, m. p. 185·5—186·5° (decomp.) (Found: C, 64·3; H, 6·8; N, 3·6; Cl, 17·2. $C_{22}H_{26}O_2NCl,HCl$ requires C, 64·7; H, 6·7; N, 3·4; Cl, 17·4%).

2-*Dimethylamino*cyclo*hexyl Benzilate*.—The chloro-ester hydrochloride (10 g.), m. p. 178—185°, was dissolved in hot water (10 c.c.) and, after 5 minutes at 100°, the crystalline solid which had precipitated was taken up in alcohol (100 c.c.) and water (20 c.c.). On cooling, the *benzilate hydrochloride* (8·8 g., 90%) separated in rods, m. p. 227—229° (decomp.) raised by one crystallisation from aqueous alcohol to 230—231° (decomp.) (Found: C, 67·7; H, 7·3. $C_{22}H_{27}O_3N,HCl$ requires C, 67·8; H, 7·2%). The free base, liberated from the powdered hydrochloride by aqueous ammonia and isolated with ether, was a straw-coloured gum which could not be crystallised. A portion in alcoholic solution was converted into the *picrate* which, crystallised from alcohol–acetone (4 : 1), formed deep yellow lustrous plates, m. p. 186—187° (Found: C, 57·9; H, 5·3. $C_{22}H_{27}O_3N,C_6H_3O_7N_3$ requires C, 57·7; H, 5·3%).

The dimethylamino-benzilate (2·8 g.) was treated with methyl iodide (8 g.) and the mixture refluxed for 1 hour. The excess of reagent was evaporated and the residue taken up in alcohol–acetone (1 : 1). Recrystallisation of the product (3·5 g., m. p. *ca.* 150°) from alcohol–ethyl acetate gave the pure *methiodide* (3 g.) as aggregates of colourless shining plates, m. p. 145—146° (Found: C, 54·0; H, 6·2; I, 24·6. $C_{23}H_{27}O_3N,CH_3I,H_2O$ requires C, 53·8; H, 6·3; I, 25·0%).

The crude methiodide (2·9 g.) was dissolved in hot aqueous methyl alcohol and shaken for 10 minutes with freshly precipitated silver chloride (1·5 mol.). The product obtained by evaporation of the filtered solution was a pale yellow friable mass which by crystallisation from acetone–methyl alcohol gave the *methochloride* in colourless plates, m. p. 217—217·5° (decomp.) (Found: C, 68·2; H, 7·7; Cl, 8·9. $C_{23}H_{27}O_3N,CH_3Cl$ requires C, 68·4; H, 7·5; Cl, 8·8%).

When the dimethylamino-benzilate (2·7 g.) dissolved in ether (4 c.c.) was treated with ethyl iodide scarcely any reaction occurred, and so the mixture was refluxed for 7—8 hours. The solvents were then evaporated, and the clear gum was dissolved in methyl alcohol and the solution cautiously diluted with water. Recrystallisation from aqueous methanol gave the pure *ethiodide* (2·6 g.) in lustrous plates, m. p. 144—145° (Found: C, 55·5; H, 6·7. $C_{23}H_{27}O_3N,C_2H_5I,CH_3OH$ requires C, 55·5; H, 6·7%).

An aqueous methyl alcoholic solution of the ethiodide (2·3 g.) was shaken with silver chloride (1·1 mols.) for ½ hour, and the filtered liquid then evaporated. On dissolving the residue in the minimum amount of methyl alcohol and diluting with acetone, the *ethochloride* (1·4 g.) crystallised as a cake of colourless prisms, which after recrystallisation and drying at 100°/18 mm. had m. p. 185—186° (decomp.) (Found: C, 68·5; H, 7·7; Cl, 8·1. $C_{23}H_{27}O_3N,C_2H_5Cl$ requires C, 69·0; H, 7·7; Cl, 8·5%).

2-*Diethylamino*cyclo*hexyl Diphenylchloroacetate Hydrochloride*.—(*a*) Molten diphenylchloroacetyl chloride (7·8 g.) supercooled to 30° was mixed with 2-diethylamino*cyclo*hexanol (5 g.). After the initial reaction and heating at 100—105° for 30 minutes, a solid product was obtained which after being refluxed and washed with acetone was crystallised from ethyl acetate containing a little methyl alcohol. The *diphenylchloroacetate hydrochloride* (7·9 g.) was finally obtained in colourless cubes, m. p. 193—194° (decomp.) after slight sintering above 191° (Found: C, 65·8; H, 7·1. $C_{24}H_{30}O_2NCl,HCl$ requires C, 66·0; H, 7·2%).

(*b*) 2-Diethylamino*cyclo*hexanol (2 g., 2 mols.) was mixed with the acid chloride (1·6 g., 1 mols.) in dry benzene (25 c.c.). After standing overnight, the nearly theoretical quantity of the amino-alcohol hydrochloride, m. p. 167—169°, had precipitated (Brunel, *loc. cit.* gives m. p. 168°). The filtrate was saturated with dry hydrogen chloride and then evaporated to dryness. The residual gum dissolved in dry acetone and diluted with ether gave the above hydrochloride (1·7 g., 68%), m. p. 190—192°.

2-*Diethylamino*cyclo*hexyl Benzilate*.—The crude chloro-ester hydrochloride (9·7 g.) was boiled with water (15 c.c.) for 2 minutes. On cooling, the *benzilate hydrochloride* separated, and when recrystallised from aqueous alcohol formed colourless prisms, m. p. 204—205° (decomp.) (Found: C, 69·0; H, 7·8; Cl, 8·5. $C_{24}H_{31}O_3N,HCl$ requires C, 69·0; H, 7·7; Cl, 8·5%).

The free *benzilate* (5·9 g.) was liberated from the powdered hydrochloride (7·1 g.) by ammonia and collected in ether (Found on a specimen distilled at 0·025 mm., air-bath at 195°: C, 75·7; H, 8·1. $C_{24}H_{31}O_3N$ requires C, 75·6; H, 8·2%). It gave a *picrate* crystallising from ethanol–acetone in star-shaped clusters of slender yellow needles, m. p. 169—169·5° (Found: C, 59·0; H, 5·65. $C_{24}H_{31}O_3N,C_6H_3O_7N_3$ requires C, 59·0; H, 5·6%). The base (2·9 g.), a straw-coloured gum, was refluxed in ether solution with methyl iodide (5 mols.) for 4 hours, and the product isolated by evaporation of the solvents was dissolved in the minimum of methyl alcohol and diluted with water. The product which separated over-night, washed first with methyl alcohol and then ether, gave a crystalline residue (1·1 g.); unchanged base (2·1 g.) was recovered from the washings. Treatment of the latter with methyl iodide in a sealed tube at 100° for 2 hours gave a further 0·7 g. of solid; total yield, 46%. The product

was difficult to recrystallise and was therefore treated with silver chloride in aqueous methyl alcohol to give, after evaporation of the filtered solution, the *methochloride*, which recrystallised from methyl alcohol–acetone in minute octahedra, m. p. 200—200·5° (decomp.) (Found : C, 69·4; H, 8·2; Cl, 8·6. $C_{24}H_{31}O_3N,CH_3Cl$ requires C, 69·5; H, 7·9; Cl, 8·2%).

γ-Phenylallyldimethylamine.—Phenyl-β-dimethylaminoethylcarbinol hydrochloride (Mannich and Heilner, *loc. cit.*) (6 g.) was treated with diphenylchloroacetyl chloride (7·4 g.) and heated to 115°, whereat the amber-coloured fluid slowly evolved hydrogen chloride for 7 hours. The product obtained by dissolution in boiling ethyl acetate and precipitation with ether crystallised from alcohol–ethyl acetate giving the required *hydrochloride* (2·9 g.) in long thin plates, m. p. 190·5—191° (Found : C, 66·9; H, 8·2; N, 6·5; Cl, 18·0. $C_{11}H_{15}N,HCl$ requires C, 66·8; H, 8·2; N, 7·1; Cl, 17·9%). Mannich and Chang (*loc. cit.*) give m. p. 147°, but in view of the manner of its preparation their compound may be the *cis*-isomeride.

The free base, liberated by ammonia and isolated with ether, was a straw-coloured oil characterised by the *picrate*, aggregates of pale yellow plates, m. p. 124—125° (Found : C, 52·2; H, 4·7. $C_{11}H_{15}N,C_6H_3O_7N_3$ requires C, 52·3; H, 4·7%). The vigorous reaction of the base with methyl iodide gave a *methiodide*, which formed pale cream plates, m. p. 182—183° after 2 crystallisations from alcohol (Found : C, 47·9; H, 6·1; I, 42·2. $C_{11}H_{15}N,CH_3I$ requires C, 47·5; H, 6·0; I, 41·9%).

When the unsaturated amine hydrochloride was heated with aqueous permanganate the odour of benzaldehyde was noticed. The salt was reduced in the presence of palladised charcoal, and γ-phenylpropyldimethylamine hydrochloride, m. p. 139—146°, obtained by crystallisation from acetone in very deliquescent needles (literature, 146°). For the amine picrate, m. p. 100—101° was observed (Mannich and Heilner found 103°).

γ-Dimethylamino-α-phenylpropyl Benzilate.—When diphenylchloroacetyl chloride (1·5 g., 1 mol.) dissolved in dry ether (20 c.c.) was slowly added to a solution of phenyl-β-dimethylaminoethylcarbinol (2 g., 2 mol.), a solid (1·2 g.) separated which was identified by its m. p. 135—136° as the amino-alcohol hydrochloride. After 12 hours the solution was filtered, treated with dry hydrogen chloride, and evaporated. The residue solidified when washed with ether, and had m. p. *ca.* 80°, but was difficult to recrystallise satisfactorily, and was therefore directly hydrolysed by heating with boiling water for 5 minutes. The *γ-dimethylaminoethyl-α-phenylpropyl benzilate* (1·76 g., 80%), isolated by treatment with ammonia and ether extraction, distilled at 0·02 mm. (bath at 175—180°), and then separated from light petroleum in asteroid clusters, m. p. 98·5—99·5° (Found : C, 76·9; H, 6·8. $C_{25}H_{27}O_3N$ requires C, 77·1; H, 6·9%).

Heating with methyl iodide gave a glassy methiodide converted by silver chloride in hot aqueous methanol into a *methochloride*, which was isolated, by evaporation and recrystallisation from acetone containing a trace of ethanol, in long slender needles, m. p. 211—212° (Found : C, 70·7; H, 7·0; Cl, 8·0. $C_{25}H_{27}O_3N,CH_3Cl$ requires C, 71·0; H, 6·9; Cl, 8·1%).

Phenyldimethylaminomethylcarbinol.—Dimethylaminoacetophenone, b. p. 122—122·5°/14—15 mm., was obtained in 60% yield from dimethylamine and bromoacetophenone in benzene (cf. v. Braun and Weissbach, *Ber.*, 1929, **62**, 2425). The amino-ketone (7·2 g.) in dry ethanol (40 c.c.) was hydrogenated at N.T.P. using platinum oxide catalyst, 70% absorption occurring in 3 hours. Complete reduction required 24 hours, after which the product was distilled, whereby the *amino-alcohol* was obtained as a pale straw-coloured oil (5·7 g., 78%), b. p. 94—97°/1 mm., $n_D^{26°}$ 1·517 (Found : 72·6; H, 9·3. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·15%). The *methiodide* crystallised from ethanol in colourless stout prisms, m. p. 226° (Found : C, 43·4; H, 5·6; I, 41·75. $C_{10}H_{15}ON,CH_3I$ requires C, 43·0; H, 5·9; I, 41·3%). Pharmacological data are given for the amino-alcohol by Alles and Knoefel (*Arch. int. Pharmacodyn.*, 1934, **47**, 96) but its preparation has not been recorded. An optically active form of the base is known from the methylation of a natural product (Men'shikov and Rubinstein, *J. Gen. Chem. Russia*, 1943, **13**, 801).

When diphenylchloroacetyl chloride (1 mol.) and the alcohol (2 mol.) reacted in ether solution, the amine *hydrochloride* separated and was obtained by crystallisation from ethanol–ethyl acetate (1 : 3) as glistening minute plates, m. p. 150—151° (Found : C, 59·7; H, 7·9. $C_{10}H_{15}ON,HCl$ requires C, 59·5; H, 8·0%). Evaporation of the ethereal filtrate treated with hydrogen chloride left a syrup which on solution in ethyl acetate gave needles, m. p. 142—143·5°; but the product was not analytically pure.

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DYSON PERRINS LABORATORY, OXFORD. [*Received, June 11th,* 1946.]

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41. *Reactions of Cellulose. Part I.*

By JOHN HONEYMAN.

The course of tritylation, tosylation, and ethylation of cellulose has been followed by determining the relative positions of the substituents and the number of glycol groups present.*

The very rapid rate of tritylation in the primary position compared with the average rate of substitution of secondary hydroxyl groups markedly decreases as the degree of substitution increases. A pronounced steric effect is noticeable as the number of secondary trityl groups increases. A monotrityl cellulose with practically all the primary and very few secondary hydroxyl groups substituted has been prepared.

For tosylation, the relative speed of primary substitution varies less, and no steric effect enters during esterification of secondary hydroxyl groups.

* The abbreviations trityl (for triphenylmethyl) and tosyl (for *p*-toluenesulphonyl) are used throughout.

The usual commercial process for ethyl cellulose manufacture is shown to be initially heterogeneous becoming homogeneous in the later stages. If the reaction is maintained heterogeneous throughout a product of somewhat different properties is obtained.

I. *Tritylation.*—Trityl cellulose was first prepared by Helferich and Koester (*Ber.*, 1924, **57**, 587) as a brown powder containing one trityl group for each anhydroglucose residue. At that time it was considered that trityl chloride reacted only with primary hydroxyl groups and hence this product was assumed to be 6-trityl cellulose. Later work, however, showed that trityl chloride was not specific for primary hydroxyl groups (*e.g.*, Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366) and, in fact, could react with compounds such as α-methylxyloside and β-methylarabinoside which contain secondary hydroxyl groups only (Hockett and Hudson, *J. Amer. Chem. Soc.*, 1931, **53**, 4457). More recently it has been shown by McIlroy (*J.*, 1946, 100) that αβ-methylxylofuranosides can give a ditrityl derivative in which the primary and one secondary hydroxyl group have been substituted. The reaction of trityl chloride with cellulose was studied more systematically by Hearon, Hiatt, and Fordyce (*J. Amer. Chem. Soc.*, 1943, **65**, 2449) who showed that tritylation in pyridine took place with little or no reduction in chain-length of the molecule. Treatment with phenyl *iso*cyanate under conditions which these workers had previously found (*ibid.*, p. 829) to effect complete substitution, followed by detritylation, gave a product with free hydroxyl where trityl groups had originally been. The position of these free hydroxyl groups was then determined by Oldham's method (*loc. cit.*) of tosylation followed by treatment with sodium iodide–acetone which Purves and co-workers (*J. Amer. Chem. Soc.*, 1939, **61**, 3458; 1942, **64**, 9) have shown to be applicable to cellulose derivatives. The results showed that the primary hydroxyl groups were tritylated about 14 times as fast as the secondaries, 90% of the former and 6·5% of the latter being simultaneously substituted.

This reaction has now been more closely studied by following the same procedure as Hearon *et al.* together with the lead tetra-acetate method of estimating the number of glycol groups which Purves (*ibid.*, 1942 ref.) has shown to be applicable to cellulose derivatives. In this paper Purves shows that for a heterogeneous reaction the number of glycol groups will be H/2 (where H = number of free secondary hydroxyl groups), *i.e.*, along the anhydroglucose chain there will be zones of complete reaction and zones with all the hydroxyl groups free; for a homogeneous reaction the number of glycol groups will be $H^2/4$, *i.e.*, completely random reaction; while if the number of glycol groups approaches H — 1 it will indicate a pronounced steric effect so that, in the extreme case, *all* the glucose residues will have one trityl group on a secondary carbon before any *one* has both secondaries substituted.

In the first series of experiments (Ia), regenerated cellulose was treated in pyridine at 100° with 2·5 times the theoretical amount of trityl chloride required for one hydroxyl group. At first the primary hydroxyl was rapidly substituted (58 times the average rate of secondary tritylation in the first two hours) but the relative rate quickly fell away until, when the number of free primary groups was small, the rates were equal (16—20 hours: 1·10—1·15 trityl groups/glucose residue). Thereafter the phenomenon (noted by Hearon *et al.*) of apparent loss of trityl was observed. It was shown that trityl groups were being removed from C_6 while substitution was still taking place on C_2 and C_3. This is considered to be due to the easier removal of primary trityl groups with hydrogen chloride in pyridine. While the product remained undissolved the number of glycol groups was found to be close to H/2, but after it became soluble the value more nearly approached H — 1 or $H^2/4$. With the low degree of secondary tritylation achieved in this case the values of H — 1 and $H^2/4$ are very close together and so it is not possible to tell whether a steric effect is operative.

When cotton cellulose was used (Ib and Ic) the product remained insoluble throughout although the degree of tritylation achieved was just as great as for regenerated cellulose. The number of glycol groups was approximately H/2 throughout, showing that with the small amount of secondary tritylation obtained (0·29 trityl/gluc.), there is no apparent steric effect. The rate of overall tritylation was less than for regenerated cellulose, but the same gradual fall in the relative rate of primary to secondary tritylation was observed.

More rapid and complete reaction was obtained by using a tenfold excess of trityl chloride (Id and Ie), but the reduction in rates already observed still obtained. Regenerated cellulose reacted more rapidly and gave a soluble product, but the derivative obtained from cotton cellulose remained undissolved. In both cases, however, the number of glycol groups present showed that, as the degree of secondary tritylation increased, a pronounced steric effect was operating, making it difficult to substitute both secondary hydroxyl groups in any glucose residue. The product obtained from regenerated cellulose after three hours' reaction is interesting,

as practically all the primary but only 3·5% of the secondary hydroxyl groups are substituted. This derivative is more nearly a true 6-trityl cellulose than any yet characterised, and it is intended to use it as an intermediate for preparing other cellulose derivatives with the substituents occupying chosen positions. Already a 2 : 3-diacetyl 6-propionyl cellulose has been prepared and found to differ from a commercial product made by random substitution.

II. *Tosylation.*—The reaction of tosyl chloride with cellulose in the presence of alkali has been investigated in a general way by Sakurada and Nakashima (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1927, **6**, 214) who found it difficult to raise the degree of esterification above that of a mono-ester even when using pyridine. Chippindale (*J. Soc. Dyers and Col.*, 1934, **50**, 144) suggested that incomplete reaction was due to an outer layer of ester preventing access of the reagents to unreacted cellulose. A very low degree of substitution was obtained by Karrer (*Helv. Chim. Acta*, 1926, **9**, 597).

The reaction has now been examined more closely by the methods described for studying tritylation. In no case was a soluble product obtained, but no difficulty was experienced in obtaining a degree of substitution corresponding to two tosyl groups/glucose residue. The results (IIa, IIb, and IIc) show that the reaction is fundamentally distinct from tritylation. The relative speed with which primary tosylation occurred did not vary so greatly when the number of free primary hydroxyl groups became small, while the glycol content approximated throughout to H/2; *i.e.*, the reaction is heterogeneous without any noticeable steric effect.

III. *Ethylation.*—The study of ethyl cellulose of different composition prepared by different methods has been described by Mahoney and Purves (*loc. cit.*), but no record has yet been made of an attempt to follow the course of ethylation.

This has now been done using the methods already described. The standard commercial method for preparing high-grade ethyl cellulose was used. Cotton cellulose was heated with sodium hydroxide solution and ethyl chloride in an autoclave. It was found that when the ethoxyl content of the product was still low it remained undissolved in the reaction mixture, but when the degree of substitution approached two ethoxyl groups/glucose residue the derivative dissolved in the reaction mixture which contained, in addition to excess ethyl chloride, ether and alcohol produced from the interaction of aqueous alkali and ethyl chloride. Examination of the glycol content of a range of products confirmed that the original heterogeneous reaction became homogeneous in the later stages. In a special preparation a very high sodium hydroxide concentration was used so that by-product formation was a minimum. The number of glycol groups, even in highly ethylated material, corresponded to H/2 showing that the reaction remained heterogeneous throughout. The properties of products obtained by this method differed in certain respects from those of the same degree of substituton obtained by the more standard method, *e.g.*, the water absorption of the heterogeneous product was lower.

Experimental.

I. *Tritylation.*—The regenerated cellulose used was prepared from a commercial cellulose acetate by treatment with aqueous ammonia. The low- and high-viscosity cellulose used were high grade commercial α-cellulose supplied by the Holden Vale Manufacturing Co. Ltd. as Bleached Cotton Linters (samples A and F).

The samples which were taken during the reactions described were purified for examination by washing free from pyridine and trityl chloride. In the case of insoluble products this was done by squeezing out as much liquid as possible, then washing with pyridine followed by dry methanol. When solution had taken place the syrup was filtered, diluted with dry methanol almost to precipitation point, and then poured in a thin stream with steady, gentle stirring into a large excess of methanol. The derivative was obtained by this method as a fine thread which was readily handled and purified by further washing. Before analysis all samples were dried to constant weight at 60°/40 mm. over calcium chloride. The trityl content and the number of free primary hydroxyl groups were determined by the methods described by Hearon *et al.* (*loc. cit.*). The number of glycol groups was found by titration with lead tetra-acetate solution under the conditions used by Mahoney and Purves (*loc. cit.*) for ethyl cellulose. Although this method was designed for products soluble in glacial acetic acid it was found to be satisfactory for insoluble products provided vigorous agitation was used, although the time required to reach the end-point was greater.

In the tables which follow the abbreviations used are :

I = insoluble.
S = soluble.
$R = \frac{\text{rate of primary tritylation}}{\text{rate of secondary tritylation}}$.
H = number of free secondary hydroxyl groups.
N = number of glycol groups found.

All the values of substituents and of free hydroxyl groups are for each anhydroglucose unit.

I(a). Regenerated cellulose (100 g.) which had been pretreated according to the method of Hearon *et al.* was added to trityl chloride (430 g., 150% excess for one hydroxyl group) in dry pyridine (1500 ml.) at 100° and the reaction mixture mechanically stirred.

Reaction time (hrs.).	Sol. or insol.	No. of trityl groups. Primary.	Secondary.	R. Period.	Average.	H.	H − 1.	H²/4.	H/2.	N.
1	I	0·16	0·00	∞	∞	2·00	1·00	1·00	1·00	0·99
2	I	0·29	0·01	26	58	1·99	0·99	0·99	1·00	0·99
3	I	0·40	0·02	22	40	1·98	0·98	0·98	0·99	0·98
4	I	0·48	0·03	16	32	1·97	0·97	0·97	0·99	0·98
6	I	0·63	0·05	15	25	1·95	0·95	0·95	0·98	0·97
8	I	0·76	0·07	13	22	1·93	0·93	0·93	0·97	0·97
12	I/S	0·86	0·09	10	19	1·91	0·91	0·91	0·96	0·93
16	S	0·94	0·16	2	12	1·84	0·84	0·85	0·92	0·85
20	S	0·95	0·20	1	10	1·80	0·80	0·81	0·90	0·81
24	S	0·94	0·21	− 2	9	1·79	0·79	0·80	0·90	0·80
36	S	0·92	0·22	− 4	8	1·78	0·78	0·79	0·89	0·78
48	S	0·85	0·24	− 7	7	1·76	0·76	0·77	0·88	0·76
96	S	0·70	0·26	−15	6	1·74	0·74	0·76	0·87	0·76

Note.—After 12 hours' reaction time the product had partly dissolved. No difference was detected in the distribution of the free hydroxyl groups in the two fractions.

I(b). Low-viscosity cellulose was used but quantities and conditions were as for I(a). The derivative remained insoluble in the reaction mixture throughout.

Reaction time (hrs.).	No. of trityl groups. Primary.	Secondary.	R (average).	H.	H/2.	H²/4.	N.
1	0·10	0·00	∞	2·00	1·00	1·00	0·99
2	0·18	0·01	36	1·99	1·00	0·99	0·99
4	0·29	0·02	29	1·98	0·99	0·98	0·99
8	0·48	0·04	24	1·96	0·98	0·96	0·97
16	0·76	0·09	17	1·91	0·96	0·91	0·96
32	0·96	0·16	12	1·84	0·92	0·85	0·92
64	0·98	0·25	8	1·75	0·88	0·77	0·86
140	0·98	0·27	7	1·73	0·87	0·75	0·87
260	0·98	0·29	7	1·71	0·86	0·73	0·85

I(c). High-viscosity cellulose was used under the conditions for I(a). The product remained insoluble throughout.

Reaction time (hrs.).	No. of trityl groups. Primary.	Secondary.	R (average).	H.	H/2.	H²/4.	N.
2	0·15	0·00	∞	2·00	1·00	1·00	1·00
24	0·63	0·07	18	1·93	0·97	0·93	0·96
98	0·86	0·12	14	1·88	0·94	0·88	0·94
218	0·99	0·20	10	1·80	0·90	0·81	0·90
338	0·99	0·24	8	1·76	0·88	0·77	0·85

I(d). Regenerated cellulose and ten times the quantity of trityl chloride theoretically required for one hydroxyl group were used under the conditions for I(a).

Reaction time (hrs.).	Sol. or insol.	No. of trityl groups. Primary.	Secondary.	R (average).	H.	H²/4.	H/2.	H − 1.	N.
½	I	0·32	0·01	64	1·99	0·99	1·00	0·99	1·00
1	I	0·51	0·02	51	1·98	0·98	0·99	0·98	0·99
2	I	0·87	0·04	44	1·96	0·96	0·98	0·96	0·97
3	S	0·98	0·07	28	1·93	0·93	0·97	0·93	0·94
4	S	0·99	0·10	20	1·90	0·90	0·95	0·90	0·90
12	S	0·99	0·32	6	1·68	0·71	0·84	0·68	0·79
24	S	0·99	0·58	4	1·42	0·50	0·71	0·42	0·48
32	S	0·98	0·74	3	1·26	0·40	0·63	0·26	0·29
38	S	0·99	0·84	2	1·16	0·34	0·58	0·16	0·19
48	S	0·99	0·90	2	1·10	0·30	0·55	0·10	0·15

I(e). Conditions were as for I(d): high-viscosity cellulose was used. Solution did not take place.

Reaction time (hrs.).	No. of trityl groups. Primary.	Secondary.	R (average).	H.	H/2.	H²/4.	H − 1.	N.
1	0·35	0·01	70	1·99	1·00	0·99	0·99	0·98
2	0·59	0·02	59	1·98	0·99	0·98	0·98	0·98
4	0·74	0·04	37	1·96	0·98	0·96	0·96	0·96
8	0·95	0·12	16	1·88	0·94	0·88	0·88	0·87
20	0·99	0·35	6	1·65	0·83	0·68	0·65	0·74
32	0·99	0·57	3	1·43	0·72	0·52	0·43	0·44
48	0·98	0·77	3	1·23	0·62	0·38	0·23	0·25
60	0·99	0·84	2	1·16	0·58	0·34	0·16	0·19

II. *Tosylation.*—The same samples of cellulose were used as described under I.

The yellowish, fibrous, and insoluble products of this series were purified by washing with pyridine followed by water before drying as before. The degree of tosylation was estimated from the sulphur content as determined by micro-analysis and the amount of primary hydroxyl groups tosylated was determined by Oldham and Rutherford's method (*J. Amer. Chem. Soc.*, 1932, **54**, 366). The number of glycol groups was determined as in I.

II(a). Pretreated regenerated cellulose (100 g.) was added to a solution of tosyl chloride (353 g., 200% excess for one hydroxyl group) in dry pyridine (1500 ml.) at 100° and the mixture mechanically stirred.

Reaction time (hrs.).	No. of tosyl groups. Primary.	Secondary.	R (average).	H.	H/2.	H²/4.	H − 1.	N.
2	0·21	0·02	21	1·98	0·99	0·98	0·98	0·99
4	0·41	0·06	14	1·94	0·97	0·94	0·94	0·96
6	0·60	0·08	15	1·92	0·96	0·92	0·92	0·95
8	0·78	0·11	14	1·89	0·95	0·89	0·89	0·93
12	0·95	0·15	13	1·85	0·93	0·86	0·85	0·92
16	0·99	0·19	10	1·81	0·91	0·82	0·81	0·89
24	1·01	0·26	—	1·74	0·87	0·76	0·74	0·86
54	1·00	0·48	—	1·52	0·76	0·58	0·52	0·74
72	1·00	0·61	—	1·39	0·70	0·48	0·39	0·67

II(b). Low-viscosity cellulose was used under the conditions of II(a).

Reaction time (hrs.).	No. of tosyl groups. Primary.	Secondary.	R (average).	H.	H/2.	H²/4.	H − 1.	N.
½	0·21	0·03	14	1·97	0·99	0·97	0·97	0·98
1	0·40	0·06	13	1·94	0·97	0·94	0·94	0·97
2	0·59	0·08	15	1·92	0·96	0·92	0·92	0·96
4	0·79	0·12	13	1·88	0·94	0·88	0·88	0·94
6	0·97	0·15	13	1·85	0·93	0·86	0·85	0·93
8	0·99	0·18	—	1·82	0·91	0·83	0·82	0·91
12	0·99	0·24	—	1·76	0·88	0·77	0·76	0·87
16	1·01	0·29	—	1·71	0·86	0·73	0·71	0·86
24	0·99	0·39	—	1·61	0·81	0·65	0·61	0·80
36	1·00	0·51	—	1·49	0·75	0·56	0·49	0·73
48	1·00	0·61	—	1·39	0·70	0·48	0·39	0·69
72	1·00	0·79	—	1·21	0·61	0·37	0·21	0·58
96	1·00	0·94	—	1·06	0·53	0·28	0·06	0·49

II(c). As II(a) except that ten times the theoretical amount of tosyl chloride for one hydroxyl was used.

Reaction time (hrs.).	No. of tosyl groups. Primary.	Secondary.	R (average).	H.	H/2.	H²/4.	H − 1.	N.
4	0·22	0·02	22	1·98	0·99	0·98	0·98	0·99
8	0·42	0·04	21	1·96	0·98	0·96	0·96	0·98
16	0·72	0·10	14	1·90	0·95	0·90	0·90	0·95
24	0·99	0·15	13	1·85	0·93	0·86	0·85	0·92
36	0·99	0·21	—	1·79	0·90	0·80	0·79	0·90
48	1·01	0·26	—	1·74	0·87	0·76	0·74	0·86
72	1·00	0·32	—	1·68	0·84	0·71	0·68	0·85
96	1·00	0·38	—	1·62	0·81	0·66	0·62	0·82

III. *Ethylation.*—Low-viscosity cellulose was used in the preparation of ethyl cellulose. The reaction was carried out in a Monel-metal-lined, steam-jacketed, mechanically stirred autoclave at 120°. Cellulose and sodium hydroxide solution were added to the autoclave which was evacuated as quickly as possible as it had been found that little degradation took place in the absence of air. Ethyl chloride was then pumped in. Sufficient hydroxide was present to ensure that the reaction mixture remained alkaline throughout, since ethyl cellulose is rapidly hydrolysed by acid although exceptionally stable towards alkali. At the end of the specified time excess of ethyl chloride was released and the mixture rapidly cooled by circulating water through the jacket. The product was purified by washing with distilled water until ion-free.

The degree of ethylation was determined by Zeisel's method, and the number of free primary hydroxyl and glycol groups was determined by the methods described by Mahoney and Purves (*loc. cit.*).

In the tables the solubility refers to whether or not the product had dissolved in the reaction mixture.

III(a). In each experiment cellulose (2 lb.) and aqueous sodium hydroxide (45%, 10 lb.) were added to the autoclave, and ethyl chloride (6·5 lb.) pumped in.

Reaction time (hrs.).	Sol. or insol.	No. of ethoxyl groups. Primary.	Secondary.	H.	H²/4.	H/2.	N.
1	I	0·41	0·49	1·51	0·57	0·76	0·70
2	I	0·61	1·01	0·99	0·24	0·55	0·59
3	I	0·69	1·25	0·75	0·14	0·38	0·39
4	S	0·77	1·39	0·61	0·09	0·31	0·12
6	S	0·85	1·67	0·33	0·03	0·17	0·04

III(b). In this series the concentration of the sodium hydroxide solution was increased to 90%; very little by-product formation took place so that the product remained undissolved throughout.

Reaction time (hrs.).	Sol. or insol.	No. of ethoxyl groups. Primary.	Secondary.	H.	$H^2/4$.	H/2.	N.
3	I	0·72	1·25	0·75	0·14	0·38	0·36
4	I	0·82	1·46	0·54	0·07	0·27	0·24
5	I	0·88	1·64	0·36	0·03	0·18	0·17
6	I	0·92	1·82	0·18	0·01	0·09	0·10

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UNIVERSITY OF LONDON, KING'S COLLEGE. [*Received, June 13th.* 1946.]

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42. *An Interpretation of the Sandmeyer Reaction. Part IX. The Behaviour of Diazotised* 2 : 4 : 6-*Trichloro- and* 2 : 4 : 6-*Tribromo-aniline towards the Sandmeyer Reagent.*

By HERBERT H. HODGSON and A. P. MAHADEVAN.

2 : 4 : 6-Trichloro- and 2 : 4 : 6-tribromo-anilines are smoothly diazotised by the nitrosyl-sulphuric–glacial acetic acid procedure (Hodgson and Walker, *J.*, 1933, 1620) and behave normally towards the Sandmeyer reagent in concentrated mineral acid solution; in dilute acid (3—4%), reduction takes place to 1 : 3 : 5-trichloro- and 1 : 3 : 5-tribromo-benzene, respectively. In boiling dilute sulphuric acid solutions containing copper sulphate, 2 : 4 : 6-trichloro- and 2 : 4 : 6-tribromo-benzenediazonium sulphates also give large yields of the respective trihalogenobenzene.

IF the mineral acid character of solutions of diazotised 2 : 4 : 6-trichloro- and 2 : 4 : 6-tribromo-aniline is maintained, the halogens are stabilised and diazo-formation is prevented (cf. also Orton, *Proc. Roy. Soc.*, 1902, **71**, 153; *J.*, 1903, **84**, 796; 1905, **87**, 99; 1907, **91**, 1554; E.P. 15,438, 1911; D.R.-P. 243,648); the behaviour, however, of the diazonium group towards the Sandmeyer reagent is now found to be determined by the acid concentration as follows. When the 2 : 4 : 6-trichloro- or -tribromo-aniline is diazotised by the direct or the inverted Hodgson and Walker method (*J.*, 1933, 1620; cf. Hodgson and Turner, *J.*, 1943, 86) and then treated with a solution of cuprous chloride or bromide in the relevant concentrated acid, replacement of the diazonium group takes place normally and smoothly with formation of 1 : 2 : 3 : 5-tetrachloro- or -tetrabromo-benzene, respectively. If, however, the concentrated acid solution of the diazonium salt is diluted with water, no diazo-oxide formation occurs (cf. the ease of diazo-oxide formation in the case of 2 : 4-dinitro-1-naphthalenediazonium sulphate), but on subsequent treatment with acid cuprous chloride or bromide as above, the diazonium group is replaced by hydrogen and 1 : 3 : 5-trichloro- or -tribromo-benzene results. In these cases the cuprous halides react as reducing agents and not as catalysts, and cupric chloride or bromide respectively is found in the ultimate reaction mixture.

This reducing behaviour of cuprous salts recalls the conversion of 2-nitro-1-naphthalenediazonium sulphate by cuprous hydroxide in glacial acetic–sulphuric acid (Hodgson, Leigh, and G. Turner, *J.*, 1942, 744) into β-nitronaphthalene. With potassium iodide, however, both 2 : 4 : 6-trichloro- and -tribromo-benzenediazonium sulphates gave normal replacement of the diazo-group by iodine, whether in concentrated or dilute mineral acid or in neutral solution; Chattaway's observation (*J.*, 1909, **95**, 869), that potassium perbromide gives 2 : 4 : 6-tribromobenzenediazonium perbromide which on heating with glacial acetic acid gives 1 : 2 : 3 : 5-tetrabromobenzene, has been confirmed.

Replacement of the diazonium group by hydrogen instead of by hydroxyl has been reported by Wroblewski (*Ber.*, 1874, **7**, 1061), who obtained some *m*-chloro- and *m*-bromo-toluene by boiling the aqueous diazonium salts of *m*-chloro- and *m*-bromo-*p*-toluidine; whereas, however, Wroblewski ascribed his results to the presence of some of the alcohol used in the preparation of the diazonium salts, an explanation endorsed by Cain (*J.*, 1906, **89**, 19) who obtained the expected halogeno-cresols in the absence of alcohol, yet the formation of 1 : 3 : 5-trichloro- and -tribromo-benzene took place at room temperature and must be ascribed to the reducing action of the cuprous salts on the very strongly electrophilic carbon atom to which the diazonium group is attached.

The great difficulty of replacing the diazonium group by hydroxyl in these trihalogeno-diazonium salts has been emphasised by Cain (*loc. cit.*), Cain and Norman (*J.*, 1906, **89**, 24),

and others (cf. E.P. 7233, 1897), who obtained only small amounts of the 2 : 4 : 6-trichloro- and -tribromo-phenols by the drastic method of dropping the diazonium solutions into mixtures of concentrated sulphuric acid and sodium sulphate at 135—145°. We have found that boiling aqueous sulphuric acid solutions of these diazonium salts with copper sulphate gave *ca.* 75% yields of 1 : 3 : 5-trichloro- and -tribromo-benzene, respectively, and we ascribe the inhibition of entry of the hydroxyl group to steric hindrance since 2 : 4 : 6-trichloro- and -tribromo-phenols are very stable substances.

Although Hantzsch and Jochem (*Ber.*, 1901, **34**, 3337) found it necessary to use an alkyl nitrite in glacial acetic acid for the diazotisation of 2 : 4 : 6-tribromoaniline sulphate, yet the diazotisation of 2 : 4 : 6-trichloro- and -tribromo-aniline proceeded smoothly by Hodgson and Walker's method (*loc. cit.*), and the respective diazonium sulphates were precipitated as clean solids on addition of ether.

Experimental.

Decomposition of 2 : 4 : 6-*Tribromobenzenediazonium Sulphate.*—(a) *In concentrated acid.* 2 : 4 : 6-Tribromoaniline (5 g.), dissolved in sulphuric acid (9·5 c.c., *d* 1·84), is treated at 0° with a solution of sodium nitrite (2 g.) in concentrated sulphuric acid (10 c.c.), and the mixture stirred into glacial acetic acid (20 c.c.), the whole being ice-cooled externally. After 45 minutes' keeping, a sample gave no precipitate on dilution with water (absence of diazo-oxide and undiazotised amine), and the solution was then rapidly stirred into one of cuprous chloride (5 g.) in hydrochloric acid (25 c.c., *d* 1·18). After the vigorous evolution of nitrogen had subsided, the mixture was gradually heated to the boil, diluted with water, and filtered; the solid was washed with hot dilute hydrochloric acid and water, and then crystallised from aqueous ethyl alcohol, 1-chloro-2 : 4 : 6-tribromobenzene being obtained in colourless needles, m. p. 91° (Jackson and Carlton, *Amer. Chem. J.*, 1904, **31**, 374, give m. p. 90—91°). When a solution of 2 : 4 : 6-tribromobenzenediazonium sulphate, obtained as above, was stirred with ether (200 c.c.) the solid diazonium compound was precipitated in glistening white crystals; alternatively, if it was treated with a solution of cuprous bromide (5 g.) in hydrobromic acid (25 c.c., *d* 1·7), 1 : 2 : 3 : 5-tetrabromobenzene (5·0 g.) was obtained; this crystallised from aqueous alcohol in colourless needles, m. p. 98° (Mayer, *Annalen*, 1866, **137**, 227, gives m. p. 98·5°) (Found: Br, 81·0. Calc. for $C_6H_2Br_4$: Br, 81·2%). Similarly, when finely powdered potassium iodide was stirred into the solution of the diazonium salt, 2 : 4 : 6-tribromoiodobenzene (6·0 g.) was obtained; it was isolated from the acid mixture by pouring it on ice, and washing the collected precipitate with saturated aqueous iodide and water, and it separated from hot ethyl alcohol in colourless needles, m. p. 105° (McCrae, *J.*, 1898, **73**, 692, gives m. p. 105·5°).

(b) *In dilute mineral acid.* 2 : 4 : 6-Tribromoaniline (5 g.) was diazotised as in (a) but the solution was poured on ice, no precipitation occurring, and then neutralised with calcium carbonate and filtered. The total volume of the solution was 300 c.c., and into it was rapidly stirred a solution of cuprous chloride (5 g.) (free from cupric salt) in hydrochloric acid (25 c.c., *d* 1·18); a vigorous evolution of nitrogen occurred, a precipitate was formed, and decomposition was completed at the boil. The precipitated 1 : 3 : 5-tribromobenzene was removed (3·2 g.) and crystallised from aqueous ethyl alcohol in colourless needles, m. p. 120° (lit. 120°) (Found: Br, 76·0. Calc. for $C_6H_3Br_3$: Br, 76·2%); alternatively, it was removed by steam-distillation. The same result was obtained when the diluted diazonium salt solution was treated with a solution of cuprous bromide (5 g.) in hydrobromic acid (25 c.c., *d* 1·7), but when it was treated with a solution of potassium iodide (5 g.) in water (25 c.c.), 2 : 4 : 6-tribromoiodobenzene was precipitated (6·0 g.); after purification and crystallisation as above, it had m. p. 105°. In both these cases, cupric chloride and cupric bromide were found in their respective solutions.

(c) *In boiling neutral solution.* 2 : 4 : 6-Tribromoaniline (1 g.) was diazotised, the solution diluted, neutralised with calcium carbonate, filtered, and boiled; a red colour developed (probably of an azo-compound) with formation of tar and only traces of steam-volatile 1 : 3 : 5-tribromobenzene.

(d) *In neutral solution with copper sulphate and cuprous oxide.* 2 : 4 : 6-Tribromoaniline (2·5 g.) was diazotised, and the solution diluted and neutralised as in (c), after which it was stirred with an aqueous solution of crystallised copper sulphate (2 g.) and admixed red cuprous oxide (1 g.) in the cold; a slight effervescence occurred which increased when the solution was heated and was completed at the boil; on steam-distillation, 1 : 3 : 5-tribromobenzene (1·5 g.) passed over.

(e) *In dilute sulphuric acid with copper sulphate.* 2 : 4 : 6-Tribromoaniline (2·5 g.) was diazotised, diluted, and neutralised as above, and to the filtered solution (150 c.c.), sulphuric acid (5 c.c., *d* 1·84) and crystallised copper sulphate (2 g.) were added; when the mixture was gradually heated to the boil, a vigorous evolution of nitrogen occurred, and 1 : 3 : 5-tribromobenzene (1·8 g.) separated; it was purified by steam-distillation.

Decomposition of 2 : 4 : 6-*Trichlorobenzenediazonium Sulphate.*—Owing to the ease of preparation of 2 : 4 : 6-tribromoaniline compared with that of 2 : 4 : 6-trichloroaniline, the above experiments were made the standards, but exactly parallel experiments were carried out with 2 : 4 : 6-trichloroaniline (0·5 g.), analogous halogeno-compounds being formed as follows: (*a*) 1 : 2 : 3 : 5-Tetrachlorobenzene, m. p. 51° (Willgerodt and Wilcke, *Ber.*, 1910, **43**, 51, give m. p. 51°); 2 : 4 : 6-trichloroiodobenzene, m. p. 54° (*lit.* 54°). (*b*) 1 : 3 : 5-Trichlorobenzene, m. p. 63—64° (Beilstein and Kurbatov, *Annalen*, 1878, **192**, 333, give m. p. 63·5°); 2 : 4 : 6-trichloroiodobenzene, m. p. 54°. (*c*) Traces of 1 : 3 : 5-trichlorobenzene. (*d*) and (*e*) 1 : 3 : 5-Trichlorobenzene.

The authors thank the Government of Madras for a Research Scholarship to one of them (A. P. M.), and Imperial Chemical Industries Ltd. (Dyestuffs Division) for gifts of chemicals.

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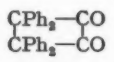
43. *The Constitution of the Dimeric Permanganate-coloured Diphenylketen.*

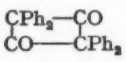
By Alexander Schönberg and Aly Sina.

For the permanganate-coloured dimeric diphenylketen obtained by pyrolysis of benzilic acid, formula (IV) is advanced. The substance reacts with piperidine giving the colourless compound (V), which on heating is reconverted into piperidine and (IV).

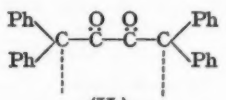
Langenbeck and Langenbeck (*Ber.*, 1928, **61**, 938) have shown that when benzilic acid is heated in the presence of a small amount of anhydrous sodium carbonate or potassium benzilate, a permanganate-coloured crystalline substance, $C_{28}H_{20}O_2$, is obtained for which they advanced formula (I), *i.e.*, that of a dimeric diphenylketen. Formula (I*a*) was proposed by Staudinger (*Ber.*, 1911, **44**, 523) for a colourless dimeric isomer.



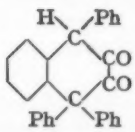
(I.)



(I*a*.)



(II.)



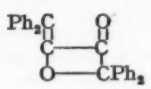
(III.)

According to its discoverers (*loc. cit.*), 1 mol. of the permanaganate-coloured substance on oxidation yielded more than one mol. of benzophenone, but no crystalline derivative could be obtained by treatment with alcoholic potash, alcoholic potassium cyanide, phosphorus pentachloride, thionyl chloride, alcoholic bromine, zinc dust and acetic acid, ethylmagnesium bromide, or phenylhydrazine, and with *o*-phenylenediamine it failed to give a quinoxaline.

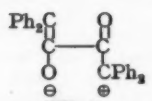
The most remarkable property of the substance is its visible colour, the intensity of which greatly exceeds that of diacetyl, benzil, or phenanthraquinone and is of the order of that of dyes.

Formula (I) was challenged by Wittig and Lupin (*Ber.*, 1928, **61**, 1630), who proposed the diradical formula (II), but this was highly improbable because the substance is very stable towards oxygen, and was finally disproved by investigation of the magnetic properties (Müller, *Ber.*, 1935, **68**, 1883). Schlenk ("Ausführliches Lehrbuch der organischen Chemie," Vol. II, p. 521, Vienna, 1939) therefore advanced formula (III), although without any experimental evidence, but this has to be discarded for the following reasons. (i) Its structure as a cyclic 1 : 2-diketone cannot explain the intensity of the absorption in the visible part of the spectrum (cf. the absorption of camphorquinone, phenanthraquinone, and acenaphthenequinone). (ii) The compound does not give a quinoxaline derivative; this cannot be explained by enolisation, for we find that the substance has no active hydrogen; also zinc-dust distillation yields no crystalline substance except diphenylmethane, whereas (III) should yield naphthalene or its phenyl derivatives. (iii) Formula (III) is inconsistent with the production of more than 1 mol. of benzophenone per mol. of compound on oxidation (see above).

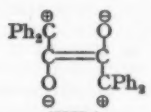
For the dimer in question, which has possibilities of resonance, we propose formula (IV), (IV*a*), or (IV*b*). The last explains the action of piperidine, in which the compound dissolves to give, after some time, an almost colourless solution, from which colourless crystals



(IV.)

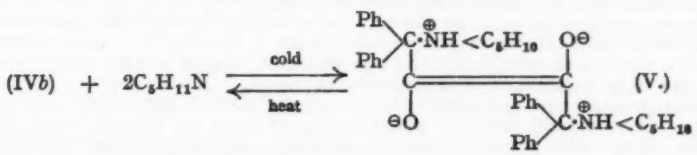


(IV*a*.)



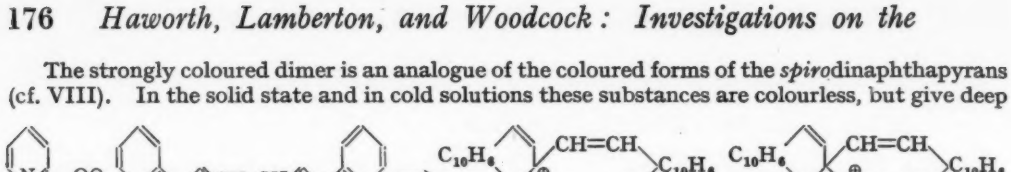
(IV*b*.)

are obtained which have the nature of an ammonium derivative; on heating, they regenerate their components. The disappearance of colour on formation of the *salt* (V) is explained by the fact that the chromophore, namely, the positively charged carbon atom, is no longer present.



According to (IV*a*) and (IV*b*), the dimer is a *C*-enol betaine, *i.e.*, one in which the positive charge is on the carbon atom and not on the nitrogen atom, as it is in the *N*-enol betaines [cf. (VI); Kröhnke, *Ber.*, 1935, **68**, 1178].

The strongly coloured dimer is an analogue of the coloured forms of the *spiro*dinaphthapyrans (cf. VIII). In the solid state and in cold solutions these substances are colourless, but give deep



(VI.) (VII; Colourless.) (VIII; Blue.) (IX.)

blue solutions on warming (VII $\rightleftharpoons$ VIII). Piperidinium salts are obtained when *spiro*dinaphthapyrans are dissolved in piperidine, the solutions being yellow whether cold or hot; (IX) is proposed for one of these piperidinium salts (Dilthey and Wizinger, *Ber.*, 1926, **59**, 1856).

A formula of type (IV) is the only one satisfactorily to explain all the foregoing phenomena.

Experimental.

Action of Piperidine on the Coloured Dimer (IV).—The dimer (1 g.) (Langenbeck and Langenbeck, *loc. cit.*) was dissolved in excess of piperidine (dried over potassium hydroxide) with the aid of gentle heat, and the red solution was left in a closed vessel for 3 days at room temperature; its colour faded gradually until it almost disappeared. Excess of piperidine was removed almost completely in a vacuum (bath temp. 80°), and the residue was mixed with petrol (b. p. 100—110°) (20 c.c.) and kept at room temperature. The colourless crystals (V) were filtered off and washed repeatedly with ligroin (b. p. 50—70°); m. p. 212° (decomp., giving a red melt). The *compound* is difficultly soluble in hot ligroin (b. p. 50—70°), hot benzene, or cold alcohol; but insoluble in water and cold dilute hydrochloric acid (Found: N, 5·0. $C_{38}H_{42}O_2N_2$ requires N, 5·0%).

Action of Heat on the Salt (V).—The salt (1 g.) was heated in a sealed evacuated vessel, fitted with a side tube ending in a small bulb, the latter being cooled in ice–salt. Heating was effected in a boiling ethyl cinnamate bath, and after 30 minutes the bulb, which contained a colourless liquid, was detached, and the liquid proved to be piperidine (picrate, from alcohol, m. p. 145° not depressed by admixture with an authentic sample; Rosenheim and Schidrowitz, *J.*, 1898, **73**, 144).

The deep violet solid which remained in the reaction vessel was dissolved in sufficient warm carbon tetrachloride; addition of alcohol (15 c.c.) precipitated some impurities, which were filtered off and the filtrate evaporated. The residue, crystallised from a small amount of ethyl acetate, proved to be (IV) (m. p. and mixed m. p. 168°; the substance gave an olive-green colour with concentrated sulphuric acid).

Irradiation of (IV).—The compound, partly dissolved and partly suspended in dry thiophen-free benzene, was exposed to sunlight (January to April) in a sealed Monax-glass tube filled with dry carbon dioxide, but was then recovered unchanged.

Fouad I University, Abbassia, Cairo. [*Received, January 2nd,* 1946.]

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44. *Investigations on the Influence of Chemical Constitution upon Toxicity. Part I. Compounds related to "Doryl."*

By Robert D. Haworth, Alex. H. Lamberton, and David Woodcock.

Little information is available regarding the influence of chemical constitution upon toxicity. The quaternary ammonium salt group was selected for preliminary investigation partly on account of the solubility of these compounds in water, and partly in view of the physiological activity of various derivatives of choline. The high toxicity of the urethane of trimethyl-2-hydroxyethylammonium chloride ("Doryl") was confirmed but a wide range of homologues and analogues described in Part I was found to exhibit lower toxicity.

This work led to an investigation, described in Part II, of aromatic compounds of the type of the methosulphate ("Prostigmine") of the *N*-methylurethane of 3-dimethylaminophenol, previously examined by Aeschlimann and Reinert, and among this group minor alterations in structure often produced major changes in toxicity. Although some of these compounds were much more lethal on subcutaneous injection than the well-known poisons brucine, curare, nicotine, and aconitine, yet others were relatively harmless.

Part III contains an account of an examination of tertiary bases of the type of the *N*-methylurethane of dimethyl-2-(3-hydroxyphenyl)ethylamine ("Miotine"). These substances were, in general, less toxic than members of the "prostigmine" group though their action was more prolonged, probably on account of their slower excretion.

The investigations have been made possible by the ready collaboration of Professor J. H. Burn, F.R.S., who carried out the pharmacological tests on "doryl" and its analogues, Dr. and Mrs. Kilby, who performed similar tests on compounds of the "prostigmine" and "miotine" types, and Professor J. R. Gaddum, F.R.S.

Compounds Structurally Related to "Doryl".—Following the discovery by Hunt and Taveau (*Brit. Med. J.*, 1906, **2**, 1788; Hygienic Lab. Bull., 1911, 73) and by Dale (*J. Pharm. Exp.*

Ther., **1914**, **6**, 147) of the powerful parasympathetic action of acetylcholine, a large number of choline derivatives were prepared. Subsequent investigation of the pharmacological potency of some of these compounds showed that, whereas the activity of acetylcholine is largely reduced because of its rapid hydrolysis by the blood esterases to choline, other more stable choline derivatives, although less intense, are more prolonged in action. For example, of five choline compounds examined by Molitor (*ibid.*, **1936**, **58**, 337) the urethane of trimethyl-2-hydroxyethylammonium chloride (Doryl) (I; $R^1 = R^2 = H$, $n = 2$) is not only the most active parasympathetically but also the most toxic. The L.D.$_{50}$ values in mg./kg. for acetylcholine and doryl reported by Molitor are given in Table I.

TABLE I.

	Intravenous.		Subcutaneous.		Oral.	
Compound.	Mice.	Rats.	Mice.	Rats.	Mice.	Rats.
Acetylcholine chloride	20	22	170	250	3000	2500
Doryl	0·3	0·1	3	4	15	40

The early pharmacological work of Hunt, Dale, Renshaw, and others (see Molitor, *loc. cit.*, for bibliography) showed that physiological activity is affected by (*a*) modification in the alkyl groups of the quaternary ammonium centre and (*b*) alteration in the number of methylene groups separating the cation and the alcoholic group, but when the present work was started there was no evidence concerning doryl analogues in which the amide hydrogen atoms were replaced by alkyl groups.

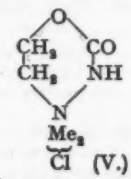
$Me_3N{\cdot}[CH_2]_n{\cdot}O{\cdot}CO{\cdot}NR^1R^2$ $\overset{\sim}{Cl}$ (I.) $\quad Me_2N{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CS{\cdot}NHMe$ (II.) $\quad Me_2N{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}SO_2Me$ (III.)

Molitor's value for the toxicity of doryl has been confirmed, and Professor J. H. Burn has shown that doryl and its *N*-methyl derivatives (I; $R^1 = Me$, $R^2 = H$, $n = 2$) show species variation. Preliminary tests showed that doryl had an L.D.$_{50}$ of 3 mg./kg. for mice, which was reduced to 0·25 mg./kg. for larger animals such as cats and dogs, and death followed from asphyxia due to blockage of the bronchial airway with mucous. It was observed that doryl has a constrictor action on the pupil of a cat but this property was not found with the homologues. The L.D.$_{50}$ values in mg./kg. for an extended range of doryl analogues on subcutaneous injection in mice are reported in the last column of Table IV, and it is clear that replacement of one or both of the amide hydrogen atoms by alkyl groups, and increase in the number of methylene groups, diminish toxicity. The data in Table IV show some alternation in toxicity with increasing chain length, but higher homologues are definitely less toxic than lower members.

The *hydrochloride* and *methiodide* of the N-*methylthiourethane* of β-*dimethylaminoethanol* (II) and the *hydrochloride* of *methyl* 2-*dimethylaminoethanesulphonate* (III) proved to have low toxicities, but as the sulphur analogues of acetylcholine and doryl were rather inaccessible further work in this direction was discontinued.

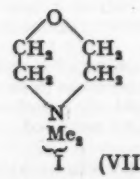
Replacement of the amide group in compounds of the doryl type by hydrazide or ether radicals resulted in substances of low toxicity. Girard-T (IV), the cyclic structure (V), obtained from *as*-dimethylhydrazine and 2-chloroethyl chloroformate, the vinyl ether (VI) of choline

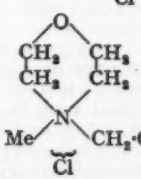
$Me_3N{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}NH_2$ $\overset{\sim}{Cl}$ (IV.)


(V.)

$Me_3N{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH{:}CH_2$ $\tilde{I}$ (VI.)

$Me_3N{\cdot}CH_2{\cdot}CH{-}CH_2$ $\tilde{I}$ (VII.)


(VIII.)


(IX.)

$Me_3NH{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}NH_2$ $\overset{\sim}{Cl}$ (X.)

$Cl{\cdot}[CH_2]_n{\cdot}O{\cdot}COCl$ (XI.)

$Cl{\cdot}[CH_2]_n{\cdot}O{\cdot}CO{\cdot}NR^1R^2$ (XII.)

iodide, and the cyclic ethers (VII), (VIII), and (IX) have toxicities of a low order, and from a miscellaneous group of compounds which have been synthesised only choline nitrate, isolated

as a crystalline perchlorate, has any appreciable toxicity. Furthermore, as the hydrochloride of the urethane of 2-dimethylaminoethanol (X) is inactive, it is concluded that high toxicity in the doryl series depends upon the presence of both urethane and quaternary ammonium groupings.

2-Chloroethyl chloroformate (XI; $n = 2$), readily obtained from carbonyl chloride and ethylene chlorohydrin (Nemirowsky, *J. pr. Chem.*, 1885, **31**, 174; Schotte, Priewe, and Roeschiesen, *Z. physiol. Chem.*, 1928, **174**, 142; Swiss Patent, 154,952), was converted by cold ammonium hydroxide into 2-chloroethyl carbamate (XII; $R^1 = R^2 = H$; $n = 2$), and by reaction with a variety of primary and secondary amines a wide variety of compounds of type (XII; $R^1 = H$ or alkyl; $R^2 =$ alkyl; $n = 2$) was prepared. 2-Chloroethyl carbamate (XII; $R^1 = R^2 = H$; $n = 2$), when heated with trimethylamine at 120—130°, gave doryl (I; $R^1 = R^2 = H$; $n = 2$) in 80% yield, but during the preparation of analogues, difficulties, arising from two causes, were sometimes encountered. Some of the quaternary chlorides were hygroscopic, purification was difficult, and conversion into the corresponding iodide by treatment with alcoholic sodium iodide was desirable. In other cases the quaternary salts were contaminated with trimethylamine hydrochloride [see Schotte *et al.* (*loc. cit.*) and Pierce (*J. Amer. Chem. Soc.*, 1928, **50**, 242)] and tedious fractional crystallisations of the corresponding iodides were often necessary.

The method employed in the synthesis of doryl has also been applied to the preparation of homologues. The glycols, prepared by Bouveault–Blanc reduction of the diethyl esters of the appropriate dibasic acids, were converted into the corresponding chlorohydrins by the action of thionyl chloride and pyridine. Treated with carbonyl chloride, the chlorohydrins gave the ω-chloroalkyl chloroformate (XI) which in turn gave the ω-chlorocarbamates (XII), and these yielded doryl homologues (I) with trimethylamine.

The reactions of 2-chloroethyl and 3-chloropropyl carbamates with triethyl-, tri-*n*-propyl-, and tri-*n*-amyl-amines were examined at temperatures varying from 15° and 180°, both in the absence and in the presence of such solvents as ether, benzene, and benzyl alcohol, but the only recognisable products were the hydrochlorides of the original tertiary amines. Substitution of the iodo- for the chloro-carbamates was sometimes useful; 2-iodoethyl carbamate reacted normally with triethylamine to give the quaternary iodide, but 2-iodoethyl *N*-phenylcarbamate yielded 3-phenyloxazolid-2-one and triethylamine hydriodide.

The syntheses of a miscellaneous group of compounds related to choline and doryl are reported in the experimental section.

Experimental.

(i) *Preparation of Chloroalkyl Chloroformates* (XI).—The preparation of 2-chloroethyl chloroformate (XI; $n = 2$) is typical. Ethylene chlorohydrin (12 g.) and carbonyl chloride (13 c.c.) were kept in a sealed tube at 15° for 70 hours. Distillation yielded 2-chloroethyl chloroformate, b. p. 152°. New compounds of this class are described in Table II.

Table II.

Chloroalkyl chloroformates.

Chloroformate.	Formula XI:	B. p.	Formula.	Found: Cl, %.	Required: Cl, %.
4-Chlorobutyl	$n = 4$	89°/10 mm.	$C_5H_8O_2Cl_2$	41·4	41·5
5-Chloropentyl	$n = 5$	125—130/15 mm.	$C_6H_{10}O_2Cl_2$	38·0	38·4
6-Chlorohexyl	$n = 6$	120/12 mm.	$C_7H_{12}O_2Cl_2$	—	—
8-Chloro-octyl	$n = 8$	130/12 mm.	$C_9H_{16}O_2Cl_2$	—	—
9-Chlorononyl	$n = 9$	137/15 mm.	$C_{10}H_{18}O_2Cl_2$	—	—
10-Chlorodecyl	$n = 10$	170/12 mm.	$C_{11}H_{20}O_2Cl_2$	29·8	30·6

(ii) *Preparation of Chloroalkyl Carbamates* (XII).—(*a*) *2-Chloroethyl carbamate* (XII; $R^1 = R^2 = H$; $n = 2$). Ammonium hydroxide (15 c.c., 15%) was gradually added with shaking and cooling to 2-chloroethyl chloroformate (XI; $n = 2$) (6·5 g.). The product was extracted with ether, dried, and most of the solvent removed. Light petroleum (b. p. 40—60°) was added until crystallisation commenced, and after 12 hours the carbamate (XII; $n = 2$) (4·6 g.), m. p. 76°, was collected.

(*b*) In other cases the following method was used. The primary or secondary amine (2·1 mols.) in benzene (5 vols.) was added with cooling and shaking to the chloroformate (1 mol.) in benzene (5 vols.). After one hour the amine hydrochloride was collected and washed with benzene, and the combined filtrate and washings were washed with dilute hydrochloric acid, dried, and the solvent removed, and the product purified either by crystallisation or by distillation under reduced pressure.

(*c*) In preparing compounds such as 2-iodoethyl carbamate, the chloro-compound and sodium iodide were refluxed in alcoholic solution for 12 hours. The sodium chloride was removed, the filtrate concentrated, and the product, isolated with ether, was purified by crystallisation from benzene.

New compounds of type (XII) are included in Table III.

TABLE III.

Chloro- and iodo-carbamates.

Carbamate.	Formula, XII :	M. p. or b. p.	Formula.	Found, %.	Required, %.
2-Iodopropyl	I for Cl; $R^1 = R^2 = H$; $n = 3$	Plates, m. p. 74—76°		—	—
2-Chloroethyl *N*-propyl-	$R^1 = C_3H_7$; $R^2 = H$; $n = 2$	B. p. 138°/ 10 mm.	$C_6H_{12}O_2NCl$	Cl, 21·4	Cl, 21·4
2-Chloroethyl *N*-allyl-	$R^1 = C_3H_5$; $R^2 = H$; $n = 2$	B. p. 130°/ 10 mm.		—	—
2-Chloroethyl *N*-benzyl-	$R^1 = C_7H_7$; $R^2 = H$; $n = 2$	Needles, m. p. 48°	$C_{10}H_{12}O_2NCl$	Cl, 16·4	Cl, 16·6
2-Iodoethyl *N*-benzyl	As above with I for Cl	Plates, m. p. 92°	$C_{10}H_{12}O_2NI$	I, 41·5	I, 41·6
2-Chloroethyl *N*-dimethyl-	$R^1 = R^2 = CH_3$; $n = 2$	B. p. 92°/ 16 mm.	$C_4H_{10}O_2NCl$	Cl, 22·7	Cl, 23·4
2-Chloroethyl *N*-diethyl	$R^1 = R^2 = C_2H_5$; $n = 2$	B. p. 100°/ 13 mm.	$C_6H_{14}O_2NCl$	Cl, 20·1	Cl, 19·8
2-Chloroethyl *N*-dipropyl	$R^1 = R^2 = C_3H_7$; $n = 2$	B. p. 135°/ 20 mm.		—	—
Piperidinium *N*-2-chloroethyl	$R^1R^2 = C_5H_{10}$; $n = 2$	B. p. 135°/ 17 mm.		—	—
2-Chloroethyl *N*-dibenzyl	$R^1 = R^2 = C_7H_7$; $n = 2$	Needles, m. p. 64°	$C_{17}H_{18}O_2NCl$	Cl, 11·1	Cl, 11·7
3-Chloropropyl	$R^1 = R^2 = H$; $n = 3$	Prisms, m. p. 58°	$C_4H_8O_2NCl$	Cl, 25·5	Cl, 26·0
4-Chlorobutyl	$R^1 = R^2 = H$; $n = 4$	Plates, m. p. 74°	$C_5H_{10}O_2NCl$	Cl, 21·4	Cl, 20·8
5-Chloropentyl	$R^1 = R^2 = H$; $n = 5$	Plates, m. p. 78°	$C_6H_{12}O_2NCl$	N, 7·8	N, 8·4
6-Chlorohexyl	$R^1 = R^2 = H$; $n = 6$	Plates, m. p. 70°	$C_7H_{14}O_2NCl$	N, 7·5	N, 7·7
8-Chloro-octyl	$R^1 = R^2 = H$; $n = 8$	Plates, m. p. 83°		—	—
9-Chlorononyl	$R^1 = R^2 = H$; $n = 9$	Plates, m. p. 77°	$C_{10}H_{20}O_2NCl$	N, 6·4	N, 6·3
10-Chlorodecyl	$R^1 = R^2 = H$; $n = 10$	Prisms, m. p. 84°	$C_{11}H_{22}O_2NCl$	Cl, 14·7	Cl, 15·1

(iii) *Preparation of Quaternary Ammonium Salts.*—(a) *Doryl* (I; $R^1 = R^2 = H$; $n = 2$). Trimethylamine (10 c.c.) and 2-chloroethyl carbamate (6 g.) were heated in a sealed tube at 110—120° for 16 hours. The crystalline contents were triturated with ether, and the product (8·3 g.) collected and crystallised from alcohol–ether.

The above method was generally applicable, but careful temperature control was often necessary, and anhydrous solvents should be used for crystallisation purposes. Conversion of chlorides into quaternary iodides was effected by treatment with cold absolute alcohol (*ca.* 5 vols.) containing sodium iodide (1·5 mols.); after one hour the sodium chloride was collected, the filtrate evaporated, and the quaternary iodide, separated from excess sodium iodide by solution in chloroform, was crystallised from alcohol or alcohol–ether.

Trimethyl-2 : 3-epoxypropylammonium chloride and *iodide* (VII) and the *urethane* of N-2-*hydroxyethylmorpholine methochloride* (IX) were prepared by similar methods.

(b) The following quaternary salts were prepared by special methods.

(i) *Urethane of triethyl-2-hydroxyethylammonium iodide.* Ethylene chlorohydrin (1·1 g.) and triethylamine (1·6 g.) were heated at 100° for 4 days and the 2-hydroxyethylammonium chloride (1 g.), after crystallisation from alcohol–ether, was shaken with carbonyl chloride (3 c.c.) in chloroform solution (3 c.c.) for 24 hours. The product was evaporated, treated with 12% ammonium hydroxide (20 c.c.) and again evaporated, and the residue extracted with absolute alcohol. The extract was refluxed with excess of sodium iodide for 10 minutes, and after removal of sodium chloride, the quaternary iodide (0·65 g.), precipitated by addition of ether, was crystallised from alcohol.

(ii) N-*Phenylurethane of triethyl-2-hydroxyethylammonium iodide.* Phenyl *iso*cyanate (1 g.) was cautiously added to 2-diethylaminoethanol (1 g.); after 10 minutes the product was heated with benzene (3 c.c.) and ethyl iodide (1·5 c.c.) in a sealed tube at 100° for 2 hours, and the ethiodide crystallised from alcohol.

(iii) 2-*Keto*-4 : 4-*dimethyl*-2 : 3 : 5 : 6-*tetrahydro*-1 : 3 : 4-*oxadiazinium chloride* (V). *as*-Dimethylhydrazine (3·5 g.) and 2-chloroethyl chloroformate (4 g.) in benzene (50 c.c.) were allowed to react in the cold for 15 minutes. The dimethylhydrazine hydrochloride was collected, the benzene removed, and the residue heated in a sealed tube for 5 hours at 110—120°.

(iv) *Ureidotrimethylammonium iodide*, $NH_2{\cdot}CO{\cdot}NH{\cdot}NMe_3\}I$. An aqueous solution of *as*-dimethylhydrazine hydrochloride (1 mol.) and potassium cyanate (2 mols.) was evaporated, and the residue extracted several times with alcohol. The *dimethylaminourea*, after crystallisation from benzene, was converted into the *methiodide* by heating with methyl iodide in a sealed tube.

Urethane of 2-dimethylaminoethanol. Dimethylamine (3 c.c.) and 2-chloroethyl carbamate (4 g.) were heated at 95° for 20 hours, and after acidification with dilute hydrochloric acid the unchanged

TABLE IV.

Homologues and analogues of "Doryl".

Compound.	In (I):	Constant.	Formula.	Found, %.	Required, %.	L.D.$_{50}$ (mg./kg.).
Urethane of trimethyl-2-hydroxyethylammonium chloride ("Doryl")	$R^1 = R^2 = H$; $n = 2$	Prisms, m. p. 207°	See (i)	—	—	3
Urethane of trimethyl-2-hydroxyethylammonium iodide	As above, with I for Cl	Prisms, m. p. 193°	See (ii)	—	—	4·5
N-Methylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = CH_3$; $R^2 = H$; $n = 2$	Needles, m. p. 173°	See (ii) and (iii)	—	—	15
N-Ethylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = C_2H_5$; $R^2 = H$; $n = 2$	M. p. 196—200°	See (iii)	—	—	60
N-Propylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = C_3H_7$; $R^2 = H$; $n = 2$	M. p. 203—207°	$C_9H_{21}O_2N_2Cl$	Cl, 15·8	Cl, 15·8	15
N-Allylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = C_3H_5$; $R^2 = H$; $n = 2$	M. p. 167—173°	$C_9H_{19}O_2N_2Cl$	Cl, 15·9	Cl, 16·0	37·5
N-Phenylurethane of trimethyl-2-hydroxyethylammonium chloride	$R^1 = C_6H_5$; $R^2 = H$; $n = 2$	Needles, m. p. 192°	$C_{13}H_{19}O_2N_2Cl$	Cl, 13·3	Cl, 13·7	37·5
N-Benzylurethane of trimethyl-2-hydroxyethylammonium iodide	$R^1 = C_7H_7$; $R^2 = H$; $n = 2$	Powder, m. p. 96°	$C_{13}H_{21}O_2N_2I$	I, 34·6	I, 34·9	62·5
N-Dimethylurethane of trimethyl-2-hydroxyethylammonium iodide	$R^1 = R^2 = CH_3$; $n = 2$	Plates, m. p. 202°	$C_8H_{19}O_2N_2I$	I, 42·0	I, 42·0	20
N-Diethylurethane of trimethyl-2-hydroxyethylammonium iodide	$R^1 = R^2 = C_2H_5$; $n = 2$	Powder, m. p. 114°	$C_{14}H_{23}O_2N_2I$	I, 38·8	I, 38·5	42·5
N-Dipropylurethane of trimethyl 2 hydroxyethylammonium chloride	$R^1 = R^2 = C_3H_7$; $n = 2$	Powder, m. p. 99°	$C_{16}H_{27}O_2N_2Cl$	Cl, 14·1	Cl, 13·3	75
Piperidylcarbamate of trimethyl-2-hydroxyethylammonium iodide	$R^1R^2 = C_5H_{10}$; $n = 2$	Plates, m. p. 178°	$C_{11}H_{23}O_2N_2I$	I, 37·2	I, 37·1	18·5
N-Dibenzylurethane of trimethyl-2-hydroxyethylammonium iodide	$R^1 = R^2 = C_7H_7$; $n = 2$	Needles, m. p. 119—121°	$C_{20}H_{27}O_2N_2I$	I, 28·0	I, 28·0	75
Urethane of trimethyl-3-hydroxypropylammonium chloride	$R^1 = R^2 = H$; $n = 3$	Prisms, m. p. 207—209°	$C_7H_{17}O_2N_2Cl$	Cl, 17·6	Cl, 18·0	37·5
Urethane of trimethyl-4-hydroxybutylammonium chloride	$R^1 = R^2 = H$; $n = 4$	Prisms, m. p. 212—213°	$C_8H_{19}O_2N_2Cl$	Cl, 16·8	Cl, 16·8	12·5
Urethane of trimethyl-5-hydroxypentylammonium chloride	$R^1 = R^2 = H$; $n = 5$	Prisms, m. p. 195—197°	$C_9H_{21}O_2N_2Cl$	Cl, 16·1	Cl, 15·8	22
Urethane of trimethyl-6-hydroxyhexylammonium chloride	$R^1 = R^2 = H$; $n = 6$	Prisms, m. p. 211—212°	$C_{10}H_{23}O_2N_2Cl$	Cl, 15·2	Cl, 14·9	100

Compound.	In (I):	Constant.	Formula.	Found, %.	Required, %.	L.D.$_{50}$ (mg./kg.).
Urethane of trimethyl-8-hydroxyoctylammonium chloride	$R^1 = R^2 = H$; $n = 8$	Plates, m. p. 205°	$C_{12}H_{27}O_2N_2Cl$	Cl, 13·5	Cl, 13·6	200
Urethane of trimethyl-9-hydroxynonylammonium chloride	$R^1 = R^2 = H$; $n = 9$	Plates, m. p. 199°	$C_{13}H_{29}O_2N_2Cl$	Cl, 12·9	Cl, 12·7	185
Urethane of trimethyl-10-hydroxydecylammonium chloride	$R^1 = R^2 = H$; $n = 10$	Prisms, m. p. 202°	$C_{14}H_{31}O_2N_2Cl$	Cl, 12·3	Cl, 12·1	75
Urethane of triethyl-2-hydroxyethylammonium iodide	$Et_3\overset{\frown}{N}\cdot CH_2\cdot CH_2\cdot O\cdot CO\cdot NH_2$ I	Prisms, m. p. 205°	$C_9H_{21}O_2N_2I$	I, 39·8	I, 40·2	395
N-Phenylurethane of triethyl-2-hydroxyethylammonium iodide	$Et_3\overset{\frown}{N}\cdot CH_2\cdot CH_2\cdot O\cdot CO\cdot NHPh$ I	Prisms, m. p. 128°	$C_{15}H_{25}O_2N_2I$	I, 32·6	I, 32·4	450
2-Keto-4 : 4-dimethyl-2 : 3 : 5 : 6-tetrahydro-1 : 3 : 4-oxadiazinium chloride	(V)	Plates, m. p. 184°	$C_5H_{11}O_2N_2Cl$	Cl, 21·4	Cl, 21·3	194
Urethane of *N*-2-hydroxyethylmorpholine methochloride	(IX)	Plates, m. p. 138°	$C_8H_{17}O_3N_2Cl$	Cl, 15·6	Cl, 15·8	194
N-Methylmorpholine methiodide	(VIII)	Needles, m. p. 235°	See (iv)	—	—	83
Vinyl ether of trimethyl-2-hydroxyethylammonium iodide	(VI)	Prisms, m. p. 177°	See (iv)	—	—	33
Trimethyl-2 : 3-epoxypropylammonium iodide	(VII)	Needles, m. p. 175°	See (v)	—	—	126
Trimethyl-2 : 3-epoxypropylammonium chloride	(VII) with Cl for I	Needles, m. p. 130—135°	See (v)	—	—	90
Choline nitrate perchlorate		M. p. 182—183°	See (vi)	—	—	30
Urethane of 2-dimethylaminoethanol hydrochloride	(X)	Plates, m. p. 144—147°	$C_5H_{12}O_2N_2Cl$	C, 35·4; H, 8·0; Cl, 20·6	C, 35·6; H, 7·8; Cl, 21·1	1000—2000
N-Methylthiourethane of trimethyl-2-hydroxyethylammonium iodide	Methiodide of (II)	Leaves, m. p. 237° (decomp.)	$C_7H_{17}ON_2SI,H_2O$	I, 39·6	I, 39·4	40
Hydrochloride of *N*-methylthiourethane of 2-dimethylaminoethanol	Hydrochloride of (II)	Polyhedra, m. p. 97°	$C_6H_{15}ON_2SCl$	Cl, 17·5	Cl, 17·9	100
Hydrochloride of methyl 2-dimethylaminoethanesulphonate	Hydrochloride of (III)	M. p. 97°	$C_5H_{14}O_3NSCl,H_2O$	Cl, 16·0; S, 14·7	Cl, 16·0; S, 14·3	100

(i) Swiss Patent, 154,952.
(ii) D.R.-P. 539,329.
(iii) Sprinson, *J. Amer. Chem. Soc.*, 1941, **63**, 2251 (published after completion of this work).
(iv) Knorr, *Annalen*, 1898, **301**, 8; *Ber.*, 1899, **32**, 738.
(v) Schmidt and Hartmann, *Annalen*, 1904, **337**, 116.
(vi) Hofmann and Hobald, *Ber.*, 1911, **44**, 1767.

carbamate was taken up in ether. The aqueous layer was made faintly alkaline to thymolphthalein and extracted with ether in a continuous extractor. Evaporation yielded crude 2-dimethylaminoethyl carbamate (1 g.) as an oil, which was converted into the *hydrochloride* by treatment with ethereal hydrogen chloride.

Salts of the N-methylthiourethane of 2-dimethylaminoethanol (II). Methyl *iso*thiocyanate (2·2 g.) and 2-dimethylaminoethanol (2·7 g.) were heated for 18 hours in a sealed tube at 110°. The product was extracted with acetone, and after removal of the solvent, the residue was heated at 100°/12 mm. for 15 minutes and then stirred with ether (10 c.c.) and the ether extract was decanted from a gum. The hydrochloride, prepared from a portion of the extract, was obtained as an oil which gradually solidified and was crystallised from alcohol–ether.

Methyl 2-dimethylaminoethanesulphonate (III). Methanesulphonyl chloride (2·6 g.) (Johnson, *J. Amer. Chem. Soc.*, 1939, **61**, 176) in ether (5 c.c.) was added dropwise to 2-dimethylaminoethanol (2 g.). The product was converted into *hydrochloride* in alcoholic solution, and the salt crystallised from alcohol–ether.

The properties of these salts and their L.D.$_{50}$ values (in mg./kg.) for subcutaneous injection into mice are included in Table IV.

Our thanks are due to R. E. Davies, M.Sc., and A. R. Pinder, B.Sc., who prepared the sulphur-containing compounds (II) and (III) and the ethers (VI, (VIII), and (IX), respectively, and to the Director General of Scientific Research (Defence) for permission to publish the results.

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45. *Investigations on the Influence of Chemical Constitution upon Toxicity. Part II. Compounds related to "Prostigmine."*

By ROBERT D. HAWORTH, ALEX. H. LAMBERTON, and DAVID WOODCOCK.

THE effect of the structure on the toxicity of the phenyltrimethylammonium iodides has been examined. The parent compound has L.D.$_{50}$ 85 mg./kg. on subcutaneous injection into mice, and the influence of simple nuclear substituents is shown in Table I, from which it is seen that the nitro-, amino-, acetamido-, methyl, aldehyde, ureido-, alcoholic, or phenolic groups, introduced into the *m*- or *p*-positions with respect to the $-NMe_3I$ group, have but minor effects on the toxicity.

In view of the lactonic structure of the powerful cardiac poisons, a quaternary salt of a basic lactone was worthy of investigation. The activity of the methiodides of 4-methyl-7-dimethylamino- and -7-diethylamino-coumarin proved to be low with L.D.$_{50}$ values of 143 and 194, respectively, and the low toxicities of all these compounds confirm a conclusion mentioned in Part I that there is apparently no simple substituent which can replace the $-O{\cdot}CO{\cdot}NHR$ group and yet preserve the high activity associated with the urethanes of quaternary ammonium salts.

TABLE I.

L.D.$_{50}$ for phenyltrimethylammonium salts.

	L.D.$_{50}$ (mg./kg.).*
Phenyltrimethylammonium iodide	85
m-Tolyltrimethylammonium iodide	125
p-Tolyltrimethylammonium iodide	180
3-Hydroxyphenyltrimethylammonium iodide	100
4-Hydroxyphenyltrimethylammonium iodide	73
3-Aminophenyltrimethylammonium iodide	186
4-Aminophenyltrimethylammonium iodide	231
3-Acetamidophenyltrimethylammonium iodide	323
4-Acetamidophenyltrimethylammonium iodide	241
3-Nitrophenyltrimethylammonium iodide	109
3-Formylphenyltrimethylammonium iodide	79
4-Formylphenyltrimethylammonium iodide	111
4-Hydroxymethylphenyltrimethylammonium iodide	139
3-Ureidophenyltrimethylammonium iodide	375
4-Ureidophenyltrimethylammonium iodide	130
3-Hydroxypyridine methiodide	1350

* These refer to subcutaneous injections into mice unless otherwise stated.

Stedman and his co-workers (*Biochem. J.*, 1926, **20**, 719; 1927, **21**, 1902; 1931, **25**, 1147; 1932, **26**, 1214; *Proc. Roy. Soc.*, 1936, *B*, **121**, 142) found that the *N*-methylurethanes of the quaternary salts of 3-dialkylaminophenols showed pharmacological properties similar to the alkaloid physostigmine. During a further investigation of these and similar compounds,

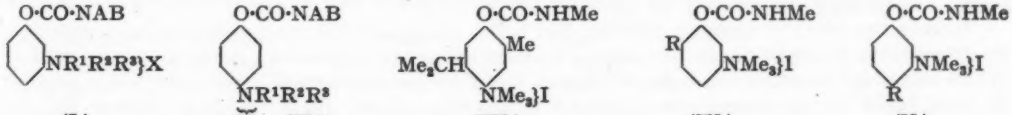
Aeschlimann and Reinert (*J. Pharm. Exp. Ther.*, 1931, **43**, 413) found that certain salts, *e.g.*, the metho-salts of the *N*-methyl- and *N*-benzyl-urethanes of 3-dimethylaminophenol with L.D.$_{80}$ of 0·1 mg./kg. on intravenous injection into mice are more toxic than physostigmine (L.D.$_{80}$, 0·5 mg./kg.). It was also shown that 3-dimethylaminophenol derivatives were more active than the 4-isomerides (Type II), and in this series, unlike the doryl class, the *N*-methylurethanes were more toxic than either *N*-dimethylurethanes or urethanes.

Since Aeschlimann and Reinert's data for the pharmacological activity of these urethanes relate to their toxicity on intravenous injection or orally, a number of these substances have been prepared, and Table II shows the L.D.$_{50}$ values obtained by subcutaneous injection. Attention was not confined entirely, however, to urethanes with *m*-orientation, and *o*-compounds were found to have greatly reduced toxicity: the L.D.$_{50}$ values for the *N*-methylurethanes of the three isomeric dimethylaminophenol methiodides were *m*-, 0·44; *p*-, 50; *o*-, 430.

TABLE II.

	L.D.$_{50}$ (mg./kg.).
Methiodide of urethane of 3-dimethylaminophenol	37
Methiodide of *N*-methylurethane of 3-dimethylaminophenol	0·44
	0·26 (rabbits)
Methochloride of *N*-methylurethane of 3-dimethylaminophenol	0·27
Ethiodide of *N*-methylurethane of 3-dimethylaminophenol	0·38
	0·13 (rabbits)
Methiodide of *N*-methylurethane of 3-diethylaminophenol	0·29
	0·15 (rabbits)
	0·17 (cats)
Methiodide of *N*-benzylurethane of 3-dimethylaminophenol	0·35
	0·20 (rabbits)
Methiodide of *N*-4-methoxybenzylurethane of 3-dimethylaminophenol	0·24
Methiodide of *N*-methylurethane of 2-dimethylaminophenol	430
Methiodide of *N*-methylurethane of 4-dimethylaminophenol	50

A new impetus to the investigation of nuclear substituents was given by the work of Stevens and Beutel (*J. Amer. Chem. Soc.*, 1941, **63**, 308), who showed that the introduction of nuclear alkyl groups, particularly *iso*propyl groups, may increase by a 100- or 1000-fold the toxicity of the *N*-methylurethanes of 4-dimethylaminophenols. For instance, the *N*-methylurethanes of 6-dimethylamino-4-*iso*propyl-*m*-cresol methiodide and the *N*-methylurethane of 5-dimethylamino-4-*iso*propyl-*o*-cresol methiodide (III) have L.D.$_{50}$ in mice of 0·22 and 1·09 mg./kg., respectively. The presence of alkyl group in the *N*-methylurethane of the isomeric 2-dimethylaminophenol methiodide, with an L.D.$_{50}$ of 430, was also accompanied with a marked increase in toxicity: the *N*-methylurethane of 3-dimethylamino-*p*-cresol methiodide has L.D.$_{50}$ of 2·0 mg./kg. In order to examine the effect of introducing alkyl groups into the quaternary salts of the methylurethanes of 3-dimethylaminophenols, which are themselves about 100 times more active than the *p*-isomerides, methods were

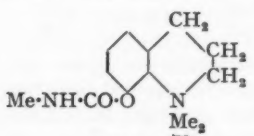


devised for the preparation of nuclear alkylated derivatives of types (IV) and (V), where R = methyl, ethyl, *iso*propyl or *cyclo*hexyl, and of polyalkylated compounds such as the methiodides of the *N*-methylurethane of 6-dimethylamino-*m*-4-xylenol and -4-*iso*propyl-*o*-cresol. The toxicities of these substances, along with our findings with the *N*-methylurethane of 5-dimethylamino-4-*iso*propyl-*o*-cresol methiodide (III) are summarised in Table III, from which the following points emerge: (i) Although the presence of methyl groups increases the toxicity in the 3-dimethylaminophenol series, the increase is fourfold as contrasted with the 10^2 to 10^3 increase observed in the 4-dimethylaminophenol series. (ii) The toxicities of the methiodides of the *N*-methylurethanes of nuclear-alkylated aminophenols reach a limiting value of 0·1 mg./kg. (iii) The maximum activity is obtained with one or more methyl substituents; ethyl, *iso*propyl, and *cyclo*hexyl groups reduce the toxicity, although the toxicities may remain high in the presence of these groups provided that methyl groups be also present. (iv) The position of the methyl group is of secondary importance, but the position of the *iso*propyl group has an enormous influence on toxicity. (v) Ethylation instead of methylation of the amino-groups is of secondary importance.

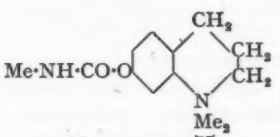
TABLE III.

Methiodide of *N*-methylurethane of—	L.D.$_{50}$ (mg./kg.).
4-Dimethylamino-*o*-cresol	0·11
3-Dimethylamino-6-ethylphenol	0·75
3-Dimethylamino-6-*iso*propylphenol	125
3-Dimethylamino-6-*cyclo*hexylphenol	175
4-Diethylamino-*o*-cresol	0·2
2-Dimethylamino-*p*-cresol	0·16
3-Dimethylamino-4-ethylphenol	0·4
3-Dimethylamino-4-*iso*propylphenol	1·0
5-Dimethylamino-*m*-cresol	0·17
5-Dimethylamino-4-*iso*propyl-*o*-cresol	0·11
6-Dimethylamino-*m*-4-xylenol	0·1
6-Dimethylamino-4-*iso*propylo-cresol	0·1
8-Hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline	45
8-Hydroxyquinoline	31
7-Hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline	0·33
N-Methyl-*N*-β-diethylaminoethyl-4-aminophenol	100
2 : 4-Tetramethyldiaminophenol	7
2 : 5-Tetramethyldiaminophenol	500—1000
6-Chloro-3-dimethylaminophenol	4

Simulation of the essential features of the *N*-methylurethane of nuclear alkylated dimethylaminophenol methiodides is obtained in the *N*-methylurethanes of 8- and 7-hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline methiodide (VI) and (VII); (VI) has a low order of toxicity (L.D.$_{50}$, 45) but (VII), with L.D.$_{50}$, 0·33 mg./kg., is among the most toxic compounds encountered during this work. The influence of the *m*-orientation of the methylurethane and basic group is again very apparent.



(VI.)



(VII.)

The effect on toxicity of chlorine as a substituent was investigated in the case of the *N*-methylurethane of 6-chloro-3-dimethylaminophenol methiodide, and the pharmacological activity was relatively low (L.D.$_{50}$, 4). Toxicity was not increased by the introduction of a second quaternary ammonium group, and the *N*-methylurethanes of 2 : 4- and 2 : 5-tetramethyldiaminophenol dimethiodides had L.D.$_{50}$ values of 7 and 500—1000, respectively; a disparity of this magnitude in the activity of two such closely related compounds is probably not real, and may be attributable to loss of methyl *iso*cyanate during the pharmacological tests.

During the toxicity tests on rabbits, Dr. Kilby observed that symptoms developed within 5—10 minutes of injection and consisted of very excessive salivation, defaecation, twitching of the voluntary muscles, muscular weakness, and slow respiration and heart rate, accompanied in most cases by anoxæmic convulsions. With fatal doses, death occurred within 10—30 minutes, and was probably due to cessation of respiration, although in a few cases it might have been due to excessive secretion of mucous in the trachea and bronchii. Post-mortem examination revealed that the liver, kidneys, and lungs were congested with petichial hæmorrhages in some rabbits. In the trachea and bronchii the mucosa were also congested and occasionally excessive amounts of mucosa were found. Intravenous injection of the *N*-methylurethane of 3-dimethylaminophenol methiodide into cats produced similar symptoms, and death was again attributed to paralysis of the respiratory centre.

Although many of the *N*-methylurethane methiodides are extremely toxic it was found, in general, that the effects of sublethal doses were transitory and complete recovery of rabbits occurred within one hour. This is probably due to rapid excretion. Aeschlimann and Reinert (*loc. cit.*) found that quaternary ammonium salts were far less toxic when administered orally than intravenously, and attributed this partly to hydrolysis *in vivo*, but more particularly to rapid elimination from the blood while absorption is still in progress. On the basis of these observations a high ratio of the oral to the subcutaneous lethal dose was also anticipated and it was found that the L.D.$_{50}$ values for oral administration of the *N*-methylurethanes of the methiodides of 3-dimethylaminophenol, 3-diethylaminophenol, and 4-dimethylamino-*o*-cresol

were respectively 16, 52, and 27 times as large as the corresponding values for subcutaneous injection.

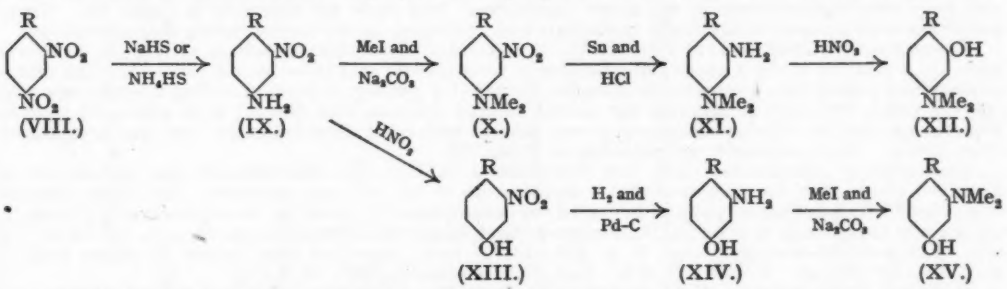
It has been shown that the hydrochlorides of the *N*-methylurethanes of 3-dimethylaminophenol, and the nuclear alkylated and chlorinated homologues did not possess marked toxicity: the L.D.$_{50}$ values were 10—100 times higher than those of the corresponding quaternary salts. On the other hand in the limited number of cases examined, the ratio of the

TABLE IV.

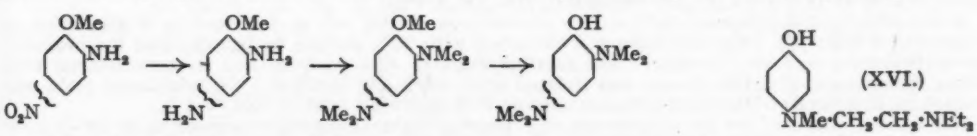
N-Methylurethane of—	L.D.$_{50}$ (mg./kg.). Subcut.	Oral.
Hydrochloride of 3-dimethylaminophenol	25	100
Hydrochloride of 2-dimethylamino-*p*-cresol	10—15	60
Hydrochloride of 3-dimethylamino-4-*iso*propylphenol	70	—
Hydrochloride of 6-dimethylamino-*o*-4-xylenol	10	50
Hydrochloride of 7-hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline	30	—
Hydriodide of 8-hydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline	5000	—
Hydrochloride of 8-hydroxyquinoline	500	—
Hydrochloride of 2 : 4-tetramethyldiaminophenol	60	—
Hydrochloride of 2 : 5-tetramethyldiaminophenol	50—75	—
Hydrochloride of 6-chloro-3-dimethylaminophenol	45	—
Dihydrobromide of *N*-methyl-*N*-β-diethylaminoethyl-4-aminophenol	16	—
Dihydrochloride of 2-hydroxy-4-dimethylaminobenzyldimethylamine	500—2500	—

oral to the subcutaneous lethal dose was approximately 4, and this suggested that hydrochlorides of tertiary bases might be excreted more slowly and therefore have more prolonged effects than quaternary ammonium salts. This aspect of the work is developed in Part III.

A few aminophenols were commercial products, but many were prepared by the following series of reaction which was also employed in the preparation of isomers and related compounds:



Phenols containing two nuclear basic centres such as 2 : 4- and 2 : 5-tetramethyldiaminophenols were prepared from 4- and 5-nitro-1-methoxyaniline by the following changes:



The phenol (XVI), containing one nuclear and one extranuclear basic centre, was also prepared from metol and 2-diethylaminoethyl chloride.

8-Hydroxy-1-methyltetrahydroquinoline was prepared from 8-hydroxyquinoline as described by Fischer (*Ber.*, 1881, **14**, 1368; 1883, **16**, 714), and the isomeric 7-hydroxy-compound was obtained by *N*-methylation of 7-hydroxytetrahydroquinoline (von Braun, *Ber.*, 1914, **47**, 2198).

EXPERIMENTAL.

The substituted phenyltrimethylammonium iodides were prepared by existing methods. The following are new:

4-*Ureidophenyltrimethylammonium iodide*, prepared by the action of methyl iodide on a cold acetone solution of 4-ureidophenyldimethylamine (Buck, *J. Amer. Chem. Soc.*, 1936, **58**, 2060), was obtained as needles, m. p. 229° (Found: I, 39·5. $C_{10}H_{16}ON_2I$ requires I, 39·5%), from alcohol.

3-*Ureidophenyldimethylamine*, prepared from potassium cyanate and *m*-aminodimethylaniline hydrochloride, crystallised from alcohol in needles, m. p. 124° (Found: C, 60·8; H, 7·5. $C_9H_{12}ON_2$ requires C, 60·3; H, 7·3%). The *methiodide* crystallised from alcohol in needles, m. p. 199° (Found: N, 12·6; I, 38·8. $C_{10}H_{16}ON_2I$ requires N, 13·1; I, 39·6%).

7-Dimethylamino-4-methylcoumarin (Pechmann and Schaal, *Ber.*, 1899, **32**, 3690) was converted into its methiodide, which separated from ethyl alcohol in lemon-yellow needles, m. p. 188—189°. The corresponding *8-dimethylamino-4-methylcoumarin*, prepared from 3-diethylaminophenol and ethyl acetoacetate, was obtained from ligroin as stout prisms, m. p. 71—72° (Found : C, 73·1; H, 7·6. $C_{14}H_{17}O_2N$ requires C, 72·6; H, 7·4%), yielding a *methiodide*, pale yellow rhombs, m. p. 177°, from water (Found : I, 33·5. $C_{15}H_{20}O_2NI$ requires I, 34·0%.).

Preparation of Dinitro-compounds (VIII) *and* m-*Nitroaniline Derivatives* (IX).—The hydrocarbons employed were obtained as follows : *m*-xylene and *p*-cymene were commercial products, ethylbenzene was obtained from acetophenone, *iso*propylbenzene was prepared from benzene, *iso*propyl bromide and aluminium chloride, and *cyclo*hexylbenzene from benzene, *cyclo*hexyl chloride, and aluminium chloride. These hydrocarbons were dinitrated as described by Ruggli, Zimmermann, and Thouvay (*Helv. Chim. Acta*, 1931, **14**, 1252), Wheeler and Harris (*J. Amer. Chem. Soc.*, 1927, **49**, 495), Weisweiller (*Monatsh.*, 1904, **21**, 39), Bogert and Stirling (*J. Org. Chem.*, 1939, **4**, 24) and Mayer and Turner (*J.*, 1929, 500), respectively. Reduction to the nitroanilines (IX) was carried out with sodium hydrogen sulphide or ammonia and hydrogen sulphide in the usual way; the bases were freed from sulphur-containing by-products by solution in 2N-hydrochloric acid.

2-*Nitro*-4-*amino*iso*propylbenzene*, obtained in 55% yield, had b. p. 135—140°/0·4 mm. and separated from ether–ligroin in yellow plates, m. p. 51—52° (Found : C, 60·0; H, 6·7. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·7%).

N-*Alkylation to Compounds of Type* (X).—The nitroaniline (1 mol.) was refluxed for 18 hours with methyl iodide (4·5 mols.) and anhydrous sodium carbonate (3·5 mols.) in methyl alcohol (5—10 mols.). In some cases alkylation resulted in the formation of tertiary bases, but in others, quaternary salts were obtained which either crystallised from the hot, filtered, alcoholic solution or were precipitated by addition of ether. It was usual to evaporate the methylation mixture to dryness, decompose the residual quaternary ammonium salt by heating at 180—200°, and distil the teriary amine at 0·5 mm. The distillate was finally warmed with acetic anhydride (1 part) for ½ hour on the water-bath, the excess anhydride removed, the residue treated with dilute hydrochloride acid, and non-basic inpurities removed in ether, and the tertiary base was recovered by addition of ammonia, isolated with ether, and purified by distillation at 0·5 mm. and finally by crystallisation

The new *compounds* described in Table V were frequently characterised as methiodides.

Reduction to Compounds of Type (XI).—The nitrodialkylaniline (X) was reduced with tin (2·5 mols.) and concentrated hydrochloric acid (7 mols.), and the amine, isolated with ether, was distilled at 0·5 mm. and frequently characterised as the acetyl derivative. New *bases* are described in Table VI. Nitroanisidines were reduced catalytically (palladium and hydrogen) to the corresponding diaminoanisoles.

Conversion into Compounds of Type (XII).—A concentrated solution of sodium nitrite (1·1 mol.) was added to a solution of the 3-aminodialkylaniline in 2N-sulphuric acid (15—16 vols.) at −5°. The diazo-solution was poured into a suspension of copper bronze (1 g. per 5 g. of base) in boiling 2N-sulphuric acid (15—16 vols.), and after 10 minutes the cooled, filtered solution was treated with excess of sodium bicarbonate and the 3-dialkylaminophenol was isolated with ether, distilled at 0·5 mm., and crystallised from ligroin. New *compounds* are described in Table VII.

Conversion of Nitroanilines (IX) *into Nitrophenols* (XIII).—The diazotisation was carried out as described above with the exception that a temperature of 10—15° was employed. The diazo-solution was poured into a boiling solution of hydrated copper sulphate (12 parts) in 2N-sulphuric acid (12 vols.). Of the new compounds of type (XIII), 3-nitro-4-ethylphenol was obtained as an oil, b. p. 142—144°/1·3 mm., and 3-*nitro*-4-iso*propylphenol*, b. p. 138—142°/1 mm., separated from ligroin in yellow prisms, m. p. 56—58° (Found : C, 59·5; H, 6·4. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1%).

Reduction of Nitrophenols (XIII) *to Aminophenols* (XIV).—This was effected in methyl alcohol with hydrogen in the presence of 15% palladium–charcoal. 3-Amino-4-ethylphenol was not isolated in pure condition, 3-*amino*-4-iso*propylphenol* crystallised from water in colourless prisms, m. p. 102—103° (Found : C, 70·8; H, 8·8. $C_9H_{13}ON$ requires C, 71·5; H, 8·6%).

Methylation to Aminophenols (XV).—This process was carried out as described in *N*-alkylation to compounds of type (V). The distillate was extracted with 20% sodium hydroxide, and the insoluble anisole derivative removed in ether. The alkaline extracts were acidified and then neutralised with sodium bicarbonate, and the phenol was isolated with ether and distilled. An additional yield was obtained by hydrolysis of the dimethylaminoanisole with hydriodic acid (5 vols., *d* 1·7).

This method was used for the preparation of 5-dimethylamino-4-*iso*propyl-*o*-cresol, m. p. 94° [hydrochloride, prisms, m. p. 215°; *acetyl* derivative, prisms, m. p. 58—60°, from ether (Found : Ac, 18·4. $C_{14}H_{21}O_3N$ requires Ac, 18·3%); *methiodide*, prisms from alcohol, m. p. 230° (Found : I, 38·4. $C_{13}H_{22}ONI$ requires I, 37·9%)], and for *7-hydroxy-1-methyl*-1 : 2 : 3 : 4-*tetrahydroquinoline*, obtained from 7-amino-1-benzoyltetrahydroquinoline (von Braun, *Ber.*, 1914, **47**, 498), as an oil, b. p. 150°/0·8 mm., which crystallised from ether–ligroin in colourless rhombs, m. p. 73—74° (Found : C, 73·3; H, 7·6. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0%).

Preparation of Urethanes and their Salts.—Methyl *iso*cyanate was prepared by Slotta's method (*Ber.*, 1925, **58**, 1320; 1927, **60**, 298). Benzyl *iso*cyanate, prepared by the action of carbonyl chloride on a toluene solution (200 c.c.) of benzylamine (6 g.) at 110—120°, was obtained as a viscous liquid, b. p. 86—88°/12 mm. (Eng. Pat. 462,182 gives b. p. 82—84°/10 mm.). *4-Methoxybenzyl* iso*cyanate*, b. p. 102—104°/1 mm., was prepared similarly (Found : N, 8·8. $C_9H_9O_2N$ requires N, 8·6%).

The dialkylaminophenol (1 mol.) and methyl *iso*cyanate (5 mols., or alternatively 1·5—2 mols. in 3 vols. of ether or benzene) were mixed with ice-cooling, and after 24 hours the solvent and excess of *iso*cyanate were removed under reduced pressure and the residue was triturated with ether. With 5-dimethylaminocarvacrol it was necessary to avoid an excess of methyl *iso*cyanate, otherwise compounds containing the diurethane group, –O·CO·NMe·CO·NHMe, were produced. The urethanes were usually purified by crystallisation from ligroin or methyl alcohol, and in some cases distillation at 0·1 mm. could be effected without decomposition.

The hydrochlorides were prepared by the action of dry hydrogen chloride in ethereal solution, and

TABLE V.

Nitrodialkylanilines.

Compound.	M. p. or b. p.	Base.	Found, %.	Required, %.	Derivative.	Formula.	Found, %.	Required, %.
2-Nitro-4-dimethylamino-1-ethylbenzene	Yellow oil, b. p. 145°/1 mm.		—	—	Methiodide; yellow plates, m. p. 180°	$C_{11}H_{17}O_2N_2I$	I, 38·5	I, 37·8
2-Nitro-4-dimethylamino-1-*iso*propylbenzene	Yellow oil, b. p. 135°/1 mm.		—	—	Methiodide; hexagonal plates, m. p. 195°	$C_{12}H_{19}O_2N_2I$	I, 36·5	I, 36·3
2-Nitro-4-dimethylamino-1-*cyclo*hexylbenzene	Yellow prisms, m. p. 55° from ligroin	$C_{14}H_{20}O_2N_2$	C, 67·6; H, 8·6	C, 67·7; H, 8·1	Methiodide; prisms, m. p. 185°	$C_{15}H_{23}O_2N_2I$	I, 33·3	I, 32·6
2-Nitro-4-diethylaminotoluene	Yellow oil, b. p. 145°/15 mm.		—	—			—	—
3-Nitro-5-dimethylaminotoluene	Red plates, m. p. 51° from ligroin	See (i)	—	—	Methiodide; plates, m. p. 178°	$C_{10}H_{15}O_2N_2I$	I, 39·0	I, 39·4
4-Nitro-6-dimethylamino-*m*-xylene	Yellow oil, b. p. 118°/0·8 mm.	See (ii)	—	—	Methiodide; needles, m. p. 162°	$C_{11}H_{17}O_2N_2I$	I, 37·3	I, 37·8
2-Nitro-6-dimethylamino-4-*iso*propyltoluene	Yellow oil, b. p. 117°/0·4 mm.		—	—			—	—
4-Chloro-3-nitrodimethylaniline	Prisms, m. p. 79° from alcohol	$C_8H_9O_2N_2Cl$ See (iii)	C, 48·6; H, 4·7	C, 47·9; H, 4·5	Methiodide; prisms, m. p. 176°	$C_9H_{12}O_2N_2ClI$	I, 36·9	I, 37·1

(i) Haibach, *J. pr. Chem.*, 1902, **65**, 246. (ii) Morgan and Micklethwait, *J.*, 1907, **41**, 365. (iii) Clemo and Smith, *J.*, 1928, 2420.

TABLE VI.

Aminodialkylamines.

Compound.	B. p.	Base.	Found, %.	Required, %.	Acetyl derivative.	Formula.	Found, %.	Required, %.
2-Amino-4-dimethylamino-1-ethylbenzene	125°/1·2 mm.		—	—	Prisms, m. p. 126°	$C_{12}H_{18}ON_2$	C, 69·7; H, 9·0	C, 69·9; H, 8·7
2-Amino-4-dimethylamino-1-*iso*propylbenzene	125°/0·8 mm.		—	—	Prisms, m. p. 118°	$C_{13}H_{20}ON_2$	C, 70·4; H, 9·0	C, 70·9; H, 9·1
2-Amino-4-dimethylamino-1-*cyclo*hexylbenzene	(M. p. 65°, from ligroin)	$C_{14}H_{22}N_2$	C, 77·0; H, 10·3	C, 77·0; H, 10·0			—	—
2-Amino-4-diethylaminotoluene	130°/1·5 mm.		—	—	Needles, m. p. 82°	$C_{13}H_{20}ON_2$	N, 13·0	N, 12·7
3-Amino-5-dimethylaminotoluene	118°/0·5 mm.		—	—	Needles, m. p. 141°	$C_{11}H_{16}ON_2$	N, 14·4	N, 14·6
4-Amino-6-dimethylamino-*m*-xylene	108°/0·4 mm.		—	—	Needles, m. p. 138°	$C_{12}H_{18}ON_2$	N, 13·8	N, 13·6
2-Amino-6-dimethylamino-4-*iso*propyltoluene	110°/0·4 mm.	$C_{12}H_{20}N_2$	N, 14·8	N, 14·5			—	—

TABLE VII.

Dialkylaminophenols.

Compound.	M. p. etc.	Base.	Found, %.	Required, %.	Derivative.	Formula.	Found, %.	Required, %.
4-Dimethylamino-*o*-cresol	Prisms, 99°	$C_9H_{13}ON$	C, 71·5; H, 8·8	C, 71·5; H, 8·7	Methiodide; m. p. 169°	$C_{10}H_{16}ONI$	I, 42·1	I, 43·0
5-Dimethylamino-2-ethylphenol	Prisms, 90°	$C_{10}H_{15}ON$	C, 72·4; H, 9·3	C, 72·7; H, 9·1	Methiodide; plates, m. p. 182°	$C_{11}H_{18}ONI$	I, 41·0	I, 41·4
5-Dimethylamino-2-*iso*propylphenol	Plates, 120°	$C_{11}H_{17}ON$	C, 73·7; H, 9·5	C, 73·7; H, 9·5	Methiodide; prisms, m. p. 178°	$C_{12}H_{20}ONI$	I, 38·7	I, 39·5
5-Dimethylamino-2-*cyclo*hexylphenol	Prisms, 120°	$C_{14}H_{21}ON$	C, 76·5; H, 9·6	C, 76·7; H, 9·6			—	—
4-Diethylamino-*o*-cresol	Prisms, 46—47°	$C_{11}H_{17}ON$	C, 74·3; H, 9·8	C, 73·7; H, 9·5	Methiodide; prisms, m. p. 173°	$C_{12}H_{20}ONI$	I, 40·0	I, 39·5
2-Dimethylamino-*p*-cresol	Prisms, 72°	$C_9H_{13}ON$ See (i)	C, 71·0; H, 8·7	C, 71·5; H, 8·7	Methiodide; plates, m. p. 170°	$C_{10}H_{16}ONI$	I, 42·2	I, 43·0
3-Dimethylamino-4-ethylphenol	(Oil, b. p. 110°/0·5 mm.).		—	—	Methiodide; prisms, m. p. 171°	$C_{11}H_{18}ONI$	I, 40·6	I, 41·4
3-Dimethylamino-4-*iso*propylphenol	Prisms, 67°	$C_{11}H_{17}ON$	C, 73·9; H, 9·9	C, 73·7; H, 9·5	Methiodide; prisms, m. p. 191°		—	—
5-Dimethylamino-*m*-cresol	Needles, 62°	$C_9H_{13}ON$	C, 71·8; H, 9·0	C, 71·5; H, 8·7	Acetyl; plates, m. p. 140°	$C_{11}H_{15}ON_2$	N, 14·4	N, 14·6
6-Dimethylamino-*m*-4-xylenol	Rhombs, 88°	$C_{10}H_{15}ON$	C, 72·4; H, 9·1	C, 72·7; H, 9·1			—	—
6-Dimethylamino-4-*iso*propyl-*o*-cresol	Prisms, 81°	$C_{12}H_{19}ON$	C, 74·5; H, 9·9	C, 74·6; H, 9·8	Methiodide; prisms, m. p. 169°	$C_{13}H_{22}ONI$	I, 37·6	I, 37·9
5-Dimethylamino-4-*iso*propyl-*o*-cresol	Prisms, 94°	See (ii)	—	—	Methiodide; prisms, m. p. 230°	$C_{13}H_{22}ONI$	I, 38·2	I, 37·9
1-Dimethylamino-2-hydroxynaphthalene	Prisms, 54°	$C_{12}H_{13}ON$	C, 77·1; H, 7·2	C, 77·0; H, 7·0			—	—
3-Hydroxypyridine			See (iii)	—	Methiodide; needles, m. p. 110°	C_6H_8ONI	I, 52·9	I, 53·5
7-Hydroxy-1-methyltetrahydroquinoline	Rhombs, 73—74°	$C_{10}H_{13}ON$	C, 73·2; H, 7·5	C, 73·6; H, 8·0				
2 : 4-Tetramethyldiaminophenol	60—62°		—	—	Dimethiodide; plates, m. p. 205°	$C_{12}H_{22}ON_2I_2$	I, 53·8	I, 54·7
2 : 5-Tetramethyldiaminophenol	84—87°		—	—	Dihydrochloride	$C_{10}H_{16}ON_2Cl_2$	Cl, 27·6	Cl, 28·0
2-Chloro-5-dimethylaminophenol	Prisms, 105°	$C_8H_{10}ONCl$	C, 56·3; H, 6·1	C, 56·1; H, 5·9			—	—
4-Amino-*N*-methyl-*N*-2′-diethylamino-ethylphenol	(B. p. 180°/0·5 mm.)	See (iv)		—	Dihydrochloride, m. p. 222°	$C_{13}H_{24}ON_2Cl_2$	Cl, 23·9	Cl, 24·0
				—	Dimethiodide; needles, m. p. 161°	$C_{15}H_{28}ON_2I_2$	I, 49·9	I, 50·2
4-Dimethylamino-2-hydroxybenzyl-dimethylamine			—	—	Dihydrochloride, m. p. 165°	$C_{11}H_{20}ON_2Cl_2$	Cl, 25·8	Cl, 26·4

(i) Mohlau, Klimmer, and Kahl, *Z. Farben u. Textilchemie*, 1902, I, 321, give m.p. 46°.
(ii) Stevens and Beutel, *J. Amer. Chem. Soc.*, 1941, **63**, 318.
(iii) Machik, *Monatsh.*, 1938, **72**, 77.
(iv) Austrian Patent, 8712/1927.

TABLE VIII.

TABLE VIII.

Urethanes.

Urethane.	M. p., etc.	Formula.	Found, %.	Required, %.	Derivative.	Formula.	Found, %.	Required, %.
N-Methylurethane of 2-dimethylaminophenol	77°. See (i)		—	—	Methiodide; m. p. 137—138°	$C_{11}H_{17}O_2N_2I$	I, 36·8	I, 37·8
N-Methylurethane of 4-dimethylaminophenol	133°. See (i)		—	—	Methiodide; m. p. 176—178°	$C_{11}H_{17}O_2N_2I$	I, 38·1	I, 37·8
Urethane of 3-dimethylaminophenol	132°. See (i)		—	—	Methiodide; m. p. 175—178°	$C_{10}H_{15}O_2N_2I$	I, 39·0	I, 39·4
N-Methylurethane of 3-dimethylaminophenol	86—89°. See (i)		—	—	Methiodide; m. p. 175°	$C_{11}H_{17}O_2N_2I$	I, 38·2	I, 37·8
					Hydrochloride; m. p. 171—172°. See (ii)			
					Ethiodide; m. p. 160°	$C_{12}H_{19}O_2N_2I$	I, 36·3	I, 36·3
N-Methylurethane of 3-diethylaminophenol	85—86°	$C_{12}H_{18}O_2N_2$	C, 65·1; H, 8·2	C, 64·9; H, 8·1	Methiodide; m. p. 140—143°. See (ii)	$C_{13}H_{21}O_2N_2I$	I, 35·0	I, 34·9
N-Benzylurethane of 3-dimethylaminophenol	See (ii)		—		Methiodide; m. p. 160°	$C_{17}H_{21}O_2N_2I$	I, 31·0	I, 30·8
N-Benzylurethane of 3-diethylaminophenol	87°	$C_{18}H_{22}O_2N_2$	C, 72·8; H, 7·5	C, 72·5; H, 7·4	Methiodide, dec. by water		—	—
N-4-Methoxybenzylurethane of 3-dimethylaminophenol	(Oil)		—	—	Methiodide; m. p. 158°	$C_{18}H_{23}O_3N_2I$	I, 29·0	I, 29·4
N-Methylurethane of 4-dimethylamino-*o*-cresol	Rhombs, m. p. 93°	$C_{11}H_{16}O_2N_2$	C, 64·0; H, 7·7	C, 63·4; H, 7·8	Methiodide; needles, m. p. 188°	$C_{12}H_{19}O_2N_2I$	I, 35·8	I, 36·0
N-Methylurethane of 5-dimethylamino-2-ethylphenol	Prisms, m. p. 97°	$C_{12}H_{18}O_2N_2$	C, 65·1; H, 8·4	C, 64·8; H, 8·1	Methiodide; prisms, m. p. 162°	$C_{13}H_{21}O_2N_2I$	I, 34·9	I, 34·8
N-Methylurethane of 5-dimethylamino-2-*iso*propylphenol	Prisms, m. p. 116°	$C_{13}H_{20}O_2N_2$	C, 66·0; H, 8·6	C, 66·1; H, 8·5	Methiodide; prisms, m. p. 179°	$C_{14}H_{23}O_2N_2I$	I, 33·1	I, 33·6
N-Methylurethane of 2-dimethylamino-3-*cyclo*hexylphenol	Prisms, m. p. 132°	$C_{16}H_{24}O_2N_2$	C, 68·9; H, 9·0	C, 69·5; H, 8·7	Methiodide; prisms, m. p. 184°	$C_{17}H_{27}O_2N_2I$	I, 31·6	I, 31·0
N-Methylurethane of 4-diethylamino-*o*-cresol	M. p. 80—82°	$C_{13}H_{20}O_2N_2$	C, 65·7; H, 8·4	C, 66·0; H, 8·5	Methiodide; m. p. 157°	$C_{14}H_{23}O_2N_2I$	I, 34·1	I, 33·6
N-Methylurethane of 2-dimethylamino-*p*-cresol	Plates, m. p. 89°	$C_{11}H_{16}O_2N_2$	C, 63·8; H, 8·0	C, 63·4; H, 7·8	Methiodide; prisms, m. p. 154°	$C_{12}H_{19}O_2N_2Cl$	I, 35·7	I, 36·0
					Hydrochloride; cubes, m. p. 156°	$C_{11}H_{17}O_2N_2Cl$	Cl, 13·8	Cl, 14·5
N-Methylurethane of 3-dimethylamino-4-ethylphenol	Prisms, m. p. 104°	$C_{13}H_{18}O_2N_2$	C, 65·2; H, 8·4; N, 12·3	C, 64·8; H, 8·1; N, 12·6	Methiodide; plates, m. p. 157°	$C_{13}H_{21}O_2N_2I$	I, 34·8	I, 34·8
N-Methylurethane of 3-dimethylamino-4-*iso*propylphenol	Prisms, m. p. 110°	$C_{13}H_{20}O_2N_2$	C, 66·2; H, 8·5; N, 11·7	C, 66·0; H, 8·5; N, 11·9	Methiodide; prisms, m. p. 167°	$C_{14}H_{23}O_2N_2I$	I, 33·4	I, 33·6
					Hydrochloride; needles, m. p. 187°	$C_{13}H_{21}O_2N_2Cl$	Cl, 13·1	Cl, 13·0
N-Methylurethane of 5-dimethylamino-*m*-cresol	Plates, m. p. 76°	$C_{11}H_{16}O_2N_2$	C, 64·7; H, 8·3	C, 63·4; H, 7·8	Methiodide; plates, m. p. 185°	$C_{12}H_{19}O_2N_2I$	I, 35·3	I, 36·0

Urethane.	M. p., etc.	Formula.	Found, %.	Required, %.	Derivative.	Formula.	Found, %.	Required, %.
N-Methylurethane of 6-dimethylamino-*m*-4-xylenol	Prisms, m. p. 95°	$C_{12}H_{18}O_2N_2$	C, 65·0; H, 8·4	C, 64·8; H, 8·1	Methiodide; plates, m. p. 162°	$C_{13}H_{21}O_2N_2I$	I, 34·6	I, 34·8
					Hydrochloride; rhombs, m. p. 181°	$C_{12}H_{19}O_2N_2Cl$	Cl, 13·4	Cl, 13·7
N-Methylurethane of 6-dimethylamino-4-*iso*propyl-*o*-cresol	Prisms, m. p. 80°	$C_{14}H_{22}O_2N_2$	C, 66·7 H, 8·8	C, 67·2; H, 8·8	Methiodide; rhombs, m. p. 175°	$C_{15}H_{25}O_2N_2I$	I, 32·6	I, 32·4
N-Methylurethane of 5-dimethylamino-4-*iso*propyl-*o*-cresol	Needles, m. p. 68°	$C_{14}H_{22}O_2N_2$	C, 67·4; H, 8·9; N, 11·3	C, 67·2; H, 8·8; N, 11·2	Methiodide; plates, m. p. 163°	See (iii)	—	—
N-Methylurethane of 1-dimethylamino-2-naphthol	M. p. 90°	$C_{14}H_{16}O_2N_2$	C, 69·3; H, 6·7	C, 68·8; H, 6·1	Does not form a methiodide.			
N-Phenylurethane of 3-hydroxypyridine	Plates, m. p. 132°	$C_{12}H_{10}O_2N_2$	C, 67·6; H, 5·3	C, 67·3; H, 4·7	Methiodide; m. p. 131°; dec. by water	$C_{13}H_{13}O_2N_2I$	I, 35·2	I, 35·6
N-Methylurethane of 8-hydroxy-1-methyltetrahydroquinoline	Prisms, m. p. 98°	$C_{12}H_{16}O_2N_2$	C, 64·5; H, 7·3	C, 65·4; H, 7·3	Methiodide; prisms, m. p. 215°	$C_{13}H_{19}O_2N_2I$	I, 35·0	I, 35·1
				—	Hydriodide; prisms, m. p. 160°	$C_{12}H_{17}O_2N_2I$	I, 35·7	I, 36·5
N-Methylurethane of 7-hydroxy-1-methyltetrahydroquinoline			—	—	Methiodide; prisms, m. p. 166°	$C_{13}H_{19}O_2N_2I$	I, 34·6	I, 35·1
					Hydrochloride; m. p. 160°	$C_{12}H_{17}O_2N_2Cl$	Cl, 13·6	Cl, 13·8
N-Methylurethane of 8-hydroxyquinoline	M. p. 178°. See (i)		—	—	Methiodide; prisms, m. p. 162°	$C_{13}H_{13}O_2N_2I$	I, 37·1	I, 36·9
				—	Hydrochloride; plates, m. p. 155°	$C_{11}H_{11}O_2N_2Cl$	Cl, 14·3	Cl, 14·8
N-Methylurethane of 2 : 4-tetramethyldiaminophenol	Cubes, m. p. 89°		—	—	Dimethiodide; prisms, m. p. 197°	$C_{14}H_{26}O_2N_2I_2$	I, 45·2	I, 48·6
				—	Dihydrochloride; prisms, m. p. 173°	$C_{12}H_{21}O_2N_2Cl_2$	Cl, 22·4	Cl, 22·9
N-Methylurethane of 2 : 5-tetramethyldiaminophenol	Rhombs, m. p. 94°	$C_{12}H_{18}O_2N_2$	C, 61·3; H, 8·5	C, 60·7; H, 8·1	Dimethiodide; prisms, m. p. 215°	$C_{14}H_{26}O_2N_2I_2$	I, 48·5	I, 48·6
					Dihydrochloride; prisms, m. p. 158°	$C_{12}H_{21}O_2N_2Cl_2$	Cl, 22·5	Cl, 22·9
N-Methylurethane of 2-chloro-5-dimethylaminophenol	Prisms, m. p. 92°		—	—	Methiodide; prisms, m. p. 159°	$C_{11}H_{16}O_2N_2ClI$	I, 34·6	I, 34·3
					Hydrochloride; prisms.	$C_{10}H_{14}O_2N_2Cl_2$	Cl, 13·0	Cl, 13·4
N-Methylurethane of 4-amino-*N*-β-diethylaminoethylphenol			—	—	Methiodide; plates, m. p. 158°	$C_{16}H_{28}O_2N_2I$	I, 29·6; N, 10·5	I, 30·1; N, 10·0
					Dihydrobromide; m. p. 164°	$C_{15}H_{27}O_2N_2Br_2$	I, 29·6; N, 9·5	Br, 36·2; N, 9·5
N-Methylurethane of 4-dimethylaminobenzyl alcohol	M. p. 68—72°		—	—	Methiodide; m. p. 199°	$C_{12}H_{19}O_2N_2I$	I, 36·0	I, 35·3

(i) Stedman, *Biochem. J.*, 1926, **20**, 728. (ii) Aeschlimann and Reinert, *loc. cit.* (iii) Stevens and Beutel, *loc. cit.*

the methiodides were obtained by the action of either (*a*) methyl iodide in cold acetone solution or (*b*) excess of methyl iodide in a sealed tube at 100°.

The urethanes and their derivatives are included in Table VIII.

Our thanks are due to Dr. Brynmor Jones and Dr. A. R. Murray who prepared the *N*-methylurethanes of 6-chloro- and 6-*cyclo*hexyl-3-dimethylaminophenols respectively, to A. R. Pinder, B.Sc., for the preparation of the *N*-methylurethane of 5-dimethylamino-4-*iso*propyl-*o*-cresol, and to the Director General of Scientific Research (Defence) for permission to publish the results.

THE UNIVERSITY, SHEFFIELD, 10.

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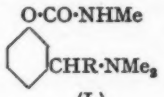
46. *Investigations on the Influence of Chemical Constitution upon Toxicity. Part III. Compounds related to "Miotine."*

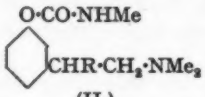
By ROBERT E. DAVIES, ROBERT D. HAWORTH, BRYNMOR JONES, and ALEX. H. LAMBERTON.

IN Parts I and II it was observed that metho-salts of the "doryl" and "prostigmine" types were usually more toxic than the salts of the corresponding tertiary bases, and that in the limited number of cases examined the ratio of toxicity by subcutaneous injection to that by oral injection was usually about 30 in the metho-salts as compared with a value of 4 with the salts of tertiary bases. In addition, it was found that the action of salts of tertiary bases was usually more prolonged than that of the corresponding quaternary salts, and these differences may be ascribed to the slower excretion of the tertiary bases.

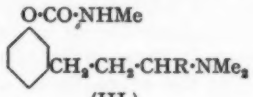
An examination has been made of the urethanes of hydroxyphenylalkylamines of types



(I.)



(II.)



(III.)

(I), (II), and (III), together with their *o*- and *p*-analogues, and nuclear-alkylated homologues; the results are recorded in Table I.

TABLE I.

L.D.$_{50}$ *for Methiodides and Hydrochlorides of* N*-Methylurethanes of Hydroxybenzyldimethylamines and Homologues.*

Name.	L.D.$_{50}$ (mg./kg.). Methiodide.	Hydrochloride.
(*a*) 2-Hydroxybenzyldimethylamine	7·2	—
Dimethyl-α-(2-hydroxyphenyl)-*n*-propylamine	10·0	40
2-Hydroxy-3-methylbenzyldimethylamine	—	300
2-Hydroxy-5-methylbenzyldimethylamine	75	120
2-Hydroxy-4-methylbenzyldimethylamine	—	145
Dimethyl-α-(4-hydroxy-*m*-tolyl)ethylamine	12	47
(*b*) 4-Hydroxybenzyldimethylamine	—	60
Dimethyl-α-(4-hydroxyphenyl)ethylamine	—	25
Dimethyl-α-(4-hydroxyphenyl)-*n*-propylamine	250—450	—
Dimethyl-β-(4-hydroxyphenyl)ethylamine	—	10
Dimethyl-γ-(4-hydroxyphenyl)-*n*-propylamine	50	5—7·5
Dimethyl-γ-(4-hydroxyphenyl)-α-methyl-*n*-propylamine	40	100 (unstable in water)
(*c*) 3-Hydroxybenzyldimethylamine	7	10
Dimethyl-α-(3-hydroxyphenyl)ethylamine	—	0·8 6·0 (oral)
Dimethyl-α-(3-hydroxyphenyl)-*n*-propylamine	4·5	2·8
Dimethyl-β-(3-hydroxyphenyl)ethylamine	7·5	3·0
Dimethyl-β-(3-hydroxyphenyl)-*n*-propylamine	0·6	0·4
Dimethyl-γ-(3-hydroxyphenyl)-α-methyl-*n*-propylamine	16	9
1-Dimethylamino-7-hydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene	20	Hydrobromide 4

The toxicities of the *N*-methylurethane of three phenolic derivatives are recorded in Table II, and the following main points emerge from the tables.

(1) In general the toxicities of hydrochlorides are not particularly high, the L.D.$_{50}$ values usually lying between 10 and 60, but two compounds are highly toxic; "miotine" (I, R = Me), previously prepared by Stedman and his co-workers (*J.*, 1929, 609; 1931, 1126; 1932, 2513;

TABLE II.

L.D.$_{50}$ *for Methiodides and Hydrochlorides of* N-*Methylurethanes of Some Hydroxytetrahydro-iso*quinolines.

Name.	L.D.$_{50}$ (mg./kg.). Methiodide.	Hydrochloride.
6-Hydroxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline	100	35
5 : 6-Dihydroxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline	60	20
6 : 7-Dihydroxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline	800	400—800

1933, 1094; *Biochem. J.*, 1929, **23**, 17; 1933, **27**, 1257; *J. Pharm. Exp. Ther.*, 1931, **41**, 259; 1937, **60**, 198; see also Part II of this series for other references), and the N-*methylurethane* of *dimethyl*-β-(3-*hydroxyphenyl*)-n-*propylamine hydrochloride* (II; R = Me) have L.D.$_{50}$ values of 0·8 and 0·4 respectively.

(2) The methiodides are far less toxic as a rule than those of the prostigmine series with the exception of the methiodide of (II; R = Me) with L.D.$_{50}$ 0·6.

(3) A *m*-orientation of the hydroxy-group with respect to the side chain favours high toxicity.

(4) In contrast to the results in the prostigmine series, the hydrochlorides of tertiary bases of types (I, (II), and (III) are frequently more toxic than the corresponding metho-salts. The alkaloid arecoline shows a similar behaviour, the hydrobromide and methiodide having L.D.$_{50}$ values of 19 and 30, respectively.

(5) Nuclear alkylation of 2-hydroxybenzyldimethylamine and its homologues is not attended by a marked increase in toxicity. Orientation difficulties were encountered during attempts to prepare alkylated 3- and 4-hydroxybenzyldimethylamines, but the properties of the *N*-methylurethane of 1-dimethylamino-7-hydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene (Table I, *c*) and the *iso*quinolines shown in Table II indicate that nuclear alkylation may lead to a reduction in toxicity in these substances.

(6) On the other hand, alkylation of the side chain leads to a substantial increase in toxicity.

New tests indicate that miotine is somewhat less toxic than was reported previously by White and Stedman (*J. Pharm. Exp. Ther.*, 1931, **41**, 259). There is very little species variation; oral toxicity is high (L.D.$_{50}$, 6), and symptoms are consistent with an accumulation of acetylcholine, due to the anti-choline esterase activity of miotine, and deaths are probably due to cessation of respiration.

2-Hydroxybenzyldimethylamine and its nuclear-methylated homologues were prepared by the Mannich reaction from phenol and the cresols (Décombe, *Compt. rend.*, 1933, **196**, 866). The Mannich reaction was also employed in the conversion of 5-ethoxyindole (Hoshino and Kotake, *Annalen*, 1935, **516**, 76) into *5-ethoxy-3-dimethylaminomethylindole*. This compound had L.D.$_{50}$, 150 mg./kg., but attempts to convert it into 5-hydroxy-3-dimethylaminomethylindole were unsuccessful.

The following series of reactions were employed extensively in the preparation of *o*-, *m*-, and *p*-ethers of type (IV).

$$MeO{\cdot}C_6H_4{\cdot}COR \longrightarrow Oxime \xrightarrow{H_2} MeO{\cdot}C_6H_4{\cdot}CHR{\cdot}NH_2 \xrightarrow[HCO_2H]{CH_2O\ and} MeO{\cdot}C_6H_4{\cdot}CHR{\cdot}NMe_2 \quad (IV.)$$

In the *o*-series, the reactions were used in cases where R = Me and Et, and in the *m*- and *p*-series compounds where R = H, Me, and Et were prepared. Miotine (I; R = Me) was obtained in good yield from 3-methoxyacetophenone, and the conversions of 2-methoxy-5-methylacetophenone and 7-methoxy-1-tetralone into *dimethyl*-α-(4-*hydroxy*-m-*tolyl*)*ethylamine* and 1-*dimethylamino*-7-*hydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene* respectively were effected.

Dimethyl-β-(4-hydroxyphenyl)ethylamine was prepared from β-(4-methoxyphenyl)ethylamine by methylation with formaldehyde and formic acid and subsequent demethylation. During attempted methylations of β-(3-methoxyphenyl)ethylamine and β-(3 : 4-dimethoxyphenyl)ethylamine by a similar procedure it was found, not unexpectedly, that ring closures occurred to 6-methoxy- and 6 : 7-dimethoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline, respectively. In order to obtain the dimethyl-β-phenylethylamine bases it was therefore necessary to methylate β-(3-methoxyphenyl)ethylamine with methyl iodide and sodium carbonate; the resulting quaternary ammonium iodide, which did not decompose smoothly on heating, was converted into the corresponding chloride, and the latter on heating gave dimethyl-β-(3-methoxyphenyl)ethylamine. γ-(4-Methoxyphenyl)propylamine, obtained from γ-(4-methoxyphenyl)butyramide, was methylated by formaldehyde to dimethyl-γ-4-methoxy-

TABLE III.

Methoxyphenyl tertiary amines.

Name.	B. p.	Derivative.	Formula.	Found, %.	Required, %.
Dimethyl-α-(2-methoxyphenyl)-*n*-propylamine	124°/16 mm.	Picrate; prisms, m. p. 146°	$C_{18}H_{24}O_8N_4$	C, 51·5; H, 5·2	C, 51·2; H, 5·2
Dimethyl-β-(3-methoxyphenyl)ethylamine	121°/13 mm.	Picrate; needles, m. p. 162°	$C_{17}H_{20}O_8N_4$	C, 49·9; H, 5·0	C, 50·0; H, 4·9
		Hydrochloride; m. p. 133°			
		Methiodide; m. p. 182°			
Dimethyl-β-(3-methoxyphenyl)-*n*-propylamine	136°/16 mm.	Methiodide; prisms, m. p. 168°	$C_{13}H_{22}ONI$	C, 46·6; H, 7·0	C, 46·6; H, 6·6
		Picrate; prisms, m. p. 141°	$C_{18}H_{22}O_8N_4$	C, 51·3; H, 5·2	C, 51·2; H, 5·2
Dimethyl-γ-(4-methoxyphenyl)-α-methyl-*n*-propylamine	155°/14 mm.	Hydrochloride; plates, m. p. 166°	$C_{13}H_{22}ONCl$	Cl, 14·9	Cl, 14·6
		Picrate; m. p. 129°			
Dimethyl-γ-(3-methoxyphenyl)-α-methyl-*n*-propylamine	155°/15 mm.				
Dimethyl-α-(4-methoxy-*m*-tolyl)ethylamine	117°/14 mm.	Picrate; prisms, m. p. 144°			
1-Dimethylamino-7-methoxytetralin	152°/17 mm.	Methiodide; needles, m. p. 141°	$C_{14}H_{22}ONI$	I, 36·0	I, 36·6
6-Methoxy-2-methyltetrahydro*iso*quinoline	138°/13 mm.	Picrate, m. p. 125°	$C_{17}H_{18}O_8N_4$	C, 50·3; H, 4·7	C, 50·2; H, 4·4
		Methiodide, m. p. 174°	$C_{12}H_{16}ONI$	I, 39·3	I, 39·8
		Hydrochloride, m. p. 172° (See i)			
5 : 6-Dimethoxy-2-methyltetrahydro*iso*quinoline	167°/13 mm.	Picrate; prisms, m. p. 133° (See ii)	$C_{18}H_{20}O_9N_4$	C, 49·5; H, 4·6	C, 49·6; H, 4·6
6 : 7-Dimethoxy-2-methyltetrahydro*iso*quinoline	M. p. 78° See (iii)	Picrate; prisms, m. p. 159°	$C_{18}H_{20}O_9N_4$	C, 49·6; H, 4·3	C, 49·6; H, 4·6

(i) Buck, *J. Amer. Chem. Soc.*, 1934, **56**, 1769, gives hydrochloride, m. p. 170°.
(ii) Haworth, *J.*, 1927, 2283, gives picrate, m. p. 164°.
(iii) Pyman, *J.*, 1909, **95**, 1266, gives m. p. 83—84°.

TABLE IV.

Phenolic tertiary bases.

Name.	B. p., etc.	Derivative.	Formula.	Found, %.	Required, %.
Dimethyl-α-(2-hydroxyphenyl)-*n*-propylamine	130°/15 mm.				
Dimethyl-α-(4-hydroxyphenyl)-*n*-propylamine	M. p. 108°		$C_{11}H_{17}ON$	C, 73·3; H, 9·3	C, 73·7; H, 9·4
		Picrate; prisms, m. p. 155°	$C_{17}H_{20}O_8N_4$	C, 50·1; H, 4·9	C, 50·0; H, 4·9
		Hydrochloride, m. p. 170°	$C_{11}H_{18}ONCl$	Cl, 16·0	Cl, 16·5
Dimethyl-β-(4-hydroxyphenyl)ethylamine	M. p. 118° See (i)	Hydriodide, m. p. 148°		—	—
Dimethyl-β-(3-hydroxyphenyl)ethylamine	M. p. 98° See (ii)	Picrate, m. p. 140°	$C_{16}H_{18}O_8N_4$	C, 48·5; H, 4·4	C, 48·7; H, 4·8
		Hydrochloride, m. p. 162°			
Dimethyl-β-(3-hydroxyphenyl)-*n*-propylamine	175°/11 mm.	Picrate, m. p. 179°	$C_{17}H_{20}O_8N_4$	C, 50·1; H, 5·1	C, 50·0; H, 4·9
		Methiodide, m. p. 168°	$C_{13}H_{20}ONI$	C, 44·7; H, 6·3	C, 44·9; H, 6·2
Dimethyl-γ-(4-hydroxyphenyl)-α-methyl-*n*-propylamine	Needles, m. p. 64°	Hydrochloride; polyhedra, m. p. 153°	$C_{13}H_{20}ONCl$	Cl, 10·8	Cl, 11·1
Dimethyl-γ-(3-hydroxyphenyl)-α-methyl-*n*-propylamine	Prisms, m. p. 83°		$C_{13}H_{19}ON$	C, 74·5; H, 9·5	C, 74·6; H, 9·7
		Hydrochloride; rods, m. p. 115°	$C_{13}H_{20}ONCl$	Cl, 15·1	Cl, 15·5
Dimethyl-α-(4-hydroxy-*m*-tolyl)ethylamine	112°/13 mm.	Hydrochloride; needles, m. p. 62°	$C_{11}H_{16}ONCl$	Cl, 16·8	Cl, 16·5
		Methiodide; needles, m. p. 250°			
1-Dimethylamino-7-hydroxytetralin	160°/15 mm.	Methiodide; plates, m. p. 150°	$C_{13}H_{20}ONI$	I, 37·6	I, 38·1
5 : 6-Dihydroxy-2-methyltetrahydro*iso*quinoline	M. p. 203°	Hydrobromide, m. p. 236°	$C_{10}H_{14}O_2NBr$	C, 46·3; H, 5·3	C, 46·1 H, 5·4
		Picrate, m. p. 190°	$C_{16}H_{16}O_9N_4$	C, 47·2; H, 4·1	C, 47·1 H, 3·9
6 : 7-Dihydroxy-2-methyltetrahydro*iso*quinoline	Prisms, m. p. 221°	See (iii)			
		Hydrobromide; m. p. 248°	$C_{10}H_{14}O_2NBr$	C, 45·8; H, 5·2	C, 46·1; H, 5·4

(i) Barger, *J.*, 1909, **95**, 2196, gives m. p. 118°.
(ii) D.R.-P. 233,069 gives m. p. 103°.
(iii) Pyman, *J.*, 1910, **97**, 264, gives m. p. 222°.

TABLE V.

N-Methylurethanes and derivatives.

N-Methylurethane of—	M. p.	Derivative.	Formula.	Found, %.	Required, %.
Dimethyl-α-(2-hydroxyphenyl)-*n*-propylamine		Methiodide, m. p. 194°	$C_{14}H_{23}O_2N_2I$	I, 32·7	I, 33·6
Dimethyl-α-(4-hydroxyphenyl)-*n*-propylamine		Methiodide, m. p. 170°	$C_{14}H_{23}O_2N_2I$	I, 32·7	I, 33·6
β-(3-Hydroxyphenyl)ethylamine		Hydrochloride, m. p. 162°	$C_{12}H_{19}O_2N_2Cl$	Cl, 13·5	Cl, 13·7
		Methiodide, m. p. 183°	$C_{12}H_{21}O_2N_2I$	I, 34·1	I, 34·9
Dimethyl-β-(3-hydroxyphenyl)-*n*-propylamine		Hydrochloride, m. p. 213°	$C_{13}H_{21}O_2N_2Cl$	Cl, 12·8	Cl, 13·0
		Methiodide, hygroscopic needles	$C_{14}H_{23}O_2N_2I$	I, 32·4	I, 33·6
Dimethyl-γ-(4-hydroxyphenyl)-*n*-propylamine		Hydrochloride; prisms, m. p. 159°	$C_{13}H_{21}O_2N_2Cl$	Cl, 12·9	Cl, 13·0
		Methiodide; prisms, m. p. 133°	$C_{14}H_{23}O_2N_2I$	I, 33·5	I, 33·6
Dimethyl-γ-(4-hydroxyphenyl)-α-methyl-*n*-propylamine		Hydrochloride; rods, m. p. 110°	$C_{14}H_{23}O_2N_2Cl$	Cl, 12·3	Cl, 12·4
		Methiodide; prisms, m. p. 129°	$C_{15}H_{25}O_2N_2I$	I, 31·7	I, 32·2
Dimethyl-γ-(3-hydroxyphenyl)-α-methyl-*n*-propylamine		Hydrochloride; needles, m. p. 130°	$C_{14}H_{23}O_2N_2Cl$	Cl, 12·7	Cl, 12·4
		Methiodide; needles, m. p. 102°	$C_{15}H_{25}O_2N_2I$	I, 31·9	I, 32·2
2-Hydroxy-5-methylbenzyldimethylamine		Hydrochloride, very hygroscopic		—	—
		Methiodide; needles, m. p. 125°	$C_{12}H_{21}O_2N_2I$	I, 35·5	I, 34·9
Dimethyl-α-(4-hydroxy-*m*-tolyl)ethylamine		Hydrochloride; needles, m. p. 150°	$C_{13}H_{21}O_2N_2Cl$	Cl, 12·7	Cl, 13·0
		Methiodide; polyhedra, m. p. 182°	$C_{14}H_{23}O_2N_2I$	I, 33·8	I, 33·6
1-Methylamino-7-hydroxytetralin	Needles, m. p. 129° from ligroin		$C_{14}H_{20}O_2N_2$	C, 67·9; H, 8·0	C, 67·7; H, 8·1
		Hydrobromide; hygroscopic prisms	$C_{14}H_{21}O_2N_2Br$	Br, 22·5	Br, 24·3
		Methiodide; prisms, m. p. 152°	$C_{15}H_{23}O_2N_2I$	I, 31·7	I, 32·5
6-Hydroxy-2-methyltetrahydro*iso*quinoline	Needles, m. p. 121°				
		Hydrochloride; needles, m. p. 165°	$C_{12}H_{17}O_2N_2Cl$	Cl, 13·8	Cl, 13·7
		Methiodide; needles, m. p. 187°	$C_{13}H_{19}O_2N_2I$	I, 34·5	I, 35·1
5 : 6-Dihydroxy-2-methyltetrahydro*iso*quinoline	Prisms, m. p. 165°		$C_{14}H_{19}O_4N_2$	C, 56·9; H, 6·4	C, 57·3; H, 6·5
		Hydrochloride, hygroscopic	$C_{14}H_{20}O_4N_2Cl$	Cl, 10·2	Cl, 10·8
		Methiodide, hygroscopic			
			$C_{14}H_{19}O_4N_2$	C, 57·2; H, 6·5	C, 57·3; H, 6·5
6 : 7-Dihydroxy-2-methyltetrahydro*iso*quinoline	Prisms, m. p. 163°				
		Hydrochloride, hygroscopic			
		Methiodide; needles, m. p. 185°	$C_{15}H_{12}O_4N_2I$	I, 28·9	I, 29·2

phenylpropylamine, and the isomeric dimethyl-β-(3-methoxyphenyl)propylamine was prepared from 3-methoxyacetophenone by the following series of reactions :

$$MeO\cdot C_6H_4\cdot CO\cdot CH_3 \xrightarrow[\text{and Zn}]{CH_2Br\cdot CO_2Et} MeO\cdot C_6H_4\cdot CMe{:}CH\cdot CO_2H \xrightarrow[\substack{\text{(iv) MeI and } Na_2CO_3,\\ \text{(v) AgCl, (vi) Heat}}]{\substack{\text{(i) } H_2,\ \text{(ii) Amide,}\\ \text{(iii) NaOCl,}}} MeO\cdot C_6H_4\cdot CHMe\cdot CH_2\cdot NMe_2$$

Dimethyl-γ-(3- and 4-methoxyphenyl)-α-methylpropylamines were obtained from the methoxybenzaldehydes by the following route :

$$MeO\cdot C_6H_4\cdot CHO \longrightarrow MeO\cdot C_6H_4\cdot CH{:}CH\cdot COMe \xrightarrow[\text{(iv) } CH_2O \text{ and } H\cdot CO_2H]{\substack{\text{(i) } H_2,\ \text{(ii) Oxime,}\\ \text{(iii) reduction,}}} MeO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CHMe\cdot NMe_2$$

The methoxy-compounds were demethylated with hydrobromic acid, and the phenol converted into the *N*-methylurethane as described in earlier Parts of the series. Excess of methyl *iso*cyanate should be avoided in the case of 2-hydroxybenzyldimethylamine otherwise a diurethane containing the O·CO·NMe·CO·NHMe group is produced.

Experimental.

5-Ethoxy-3-dimethylaminomethylindole.—5-Ethoxyindole (2·5 g.), dimethylamine hydrochloride (2·3 g.), and sodium acetate (1 g.) were dissolved in a mixture of acetic acid (3·5 g.) and 40% formaldehyde (1 c.c.). The brown solution gradually deposited a white solid, and after 18 hours the *indole*, precipitated by the addition of potassium hydroxide, was collected (2·3 g.) and crystallised from aqueous acetone; colourless needles, m. p. 146° (Found : C, 71·7; H, 8·1. $C_{13}H_{18}ON_2$ requires C, 71·6; H, 8·3%), were obtained. The *hydrochloride* separated from alcohol-ether in colourless prisms, m. p. 150° (Found : Cl, 13·9. $C_{13}H_{19}ON_2Cl$ requires Cl, 14·0%).

The aldehydes and ketones were prepared by methods described in the literature. 3-Methoxybenzylacetone, which is new, was prepared by catalytic reduction of 3-methoxybenzylideneacetone; it was an oil, b. p. 164—166°/10 mm., giving a *semicarbazone*, which separated from alcohol in needles, m. p. 125° (Found : C, 61·5; H, 7·2. $C_{12}H_{17}O_2N_3$ requires C, 61·4; H, 7·2%).

The oximes were prepared by standard methods. The following crystalline oximes are new : *2-Methoxypropiophenone oxime*, prisms, m. p. 87° from methyl alcohol (Found : C, 67·0; H, 6·9. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·2%); *4-methoxybenzylacetoxime*, long needles, m. p. 76° (Found : N, 8·0. $C_{10}H_{13}O_2N$ requires N, 7·8%) from alcohol; *7-methoxy-1-tetralone oxime*, stout prisms, m. p. 87° from ligroin (Found : C, 69·3; H, 7·1. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8%).

Of the acid amides, *β-3-methoxyphenylbutyramide*, m. p. 72° (Found : C, 68·0; H, 7·8. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%), was new. The primary amines were frequently methylated to the tertiary bases without further purification, but in a few cases new primary amines were characterised. The following were obtained by reduction of the corresponding oxime with 4% sodium amalgam : α-(2-Methoxyphenyl)propylamine, an oil, b. p. 128°/18 mm., yielding a *picrate*, which separated from alcohol in yellow prisms, m. p. 160° (Found : C, 48·3; H, 4·4. $C_{16}H_{18}O_8N_4$ requires C, 48·7; H, 4·6%). α-(4-Methoxy-*m*-tolyl)ethylamine, an oil, b. p. 120°/14 mm., gave a *picrate*, yellow rhombs from alcohol, m. p. 197° (Found : C, 48·5; H, 4·5). 1-Amino-7-methoxytetralin, b. p. 162—165°/16 mm., gave a *hydrochloride* which separated from alcohol in hexagonal plates, m. p. 233° (Found : Cl, 17·1. $C_{11}H_{16}ONCl$ requires Cl, 16·7%). γ-(4-Methoxyphenyl)-α-methyl-*n*-propylamine, b. p. 165°/16 mm., gave a picrate, m. p. 129°, and a *hydrochloride*, plates, m. p. 129° (Found : Cl, 16·0. $C_{11}H_{18}ONCl$ requires Cl, 16·5%). γ-(3-Methoxyphenyl)-α-methyl-*n*-propylamine, b. p. 148°/11 mm., gave a *picrate*, m. p. 154° (Found : C, 50·4; H, 5·0. $C_{17}H_{20}O_8N_4$ requires C, 50·0; H, 4·9%). The last two bases were prepared by the action of sodium hypochlorite on the corresponding acid amides.

Conversion of Primary into Tertiary Amines.—The primary amine (1 mol.) was mixed with 90% formic acid (5 mols.) and 35—40% aqueous formaldehyde (2·2 mols.) and refluxed for 1 hour after the evolution of carbon dioxide had ceased (usually 2—3 hours in all). The mixture was made acid to Congo-red by addition of dilute hydrochloric acid, neutral substances were removed in ether, and the tertiary base was liberated with sodium hydroxide and isolated with ether. New methoxy tertiary bases are described in Table III.

Demethylation to phenolic tertiary amines was effected by 5—6 hours' boiling with constant-boiling hydrobromic acid (5 vols.); most of the acid was removed under reduced pressure, just sufficient solid potassium hydroxide added to give a solution alkaline to phenolphthalein, and the phenol isolated with ether. New phenolic tertiary *amines* and the *urethanes*, prepared by the methods described in Part II, and the *methiodides* and *hydrochlorides* are described in Tables IV and V respectively.

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47. *Preparation and Properties of Some Long-chain Aliphatic Amines.*

By E. T. Borrows, (Mrs.) B. M. C. Hargreaves, J. E. Page, J. C. L. Resuggan, and F. A. Robinson.

A series of primary, secondary, and tertiary aliphatic amines containing between 8 and 30 carbon atoms were prepared and tested for antibacterial activity. Those with from 17 to 20 carbon atoms proved to be highly active *in vitro* against *Streptococcus hæmolyticus* and *Staphylococcus aureus*, and several inhibited the growth of *Mycobacterium tuberculosis*. The dissociation constants of 17 secondary and tertiary amines were measured by an electrometric method, but there appeared to be no correlation between these constants and antibacterial activities of the compounds.

Adams and Stanley (*J. Pharmacol.*, 1932, **45**, 121) found that a number of long-chain fatty acids had a marked inhibitory effect on the growth of the tubercle bacillus, the maximum effect being produced with compounds containing 16 or 17 carbon atoms. The activity increased, too, as the carboxyl group was displaced towards the centre of the molecule. Active compounds also resulted when the carboxyl group was replaced by a dialkylaminomethyl group. Robinson (*J.*, 1940, 508) reported the preparation of branched-chain fatty acids even more potent than those of Adams and Stanley, the most effective being 3-methyl-3-*n*-octyl-*n*-undecoic acid. Following a suggestion by Mr. G. Newbery, of May & Baker, Ltd., it was decided to prepare a number of long-chain amines analogous to the fatty acids of Adams and Stanley, and test their activity on the tubercle bacillus and other micro-organisms. Fuller (*Biochem. J.*, 1942, **36**, 548) reported that primary aliphatic amines containing 9 to 18 carbon atoms inhibited the growth of a number of micro-organisms, and that the activity increased with chain length up to a certain point and then decreased. He suggested that surface active properties might be responsible for the biological activity, and that it would be of interest to determine the activity of amines with branched chains. Fuller also tested a number of amidines, guanidines, and quaternary bases, and found that the decreased basicity of the amines made them relatively more effective against Gram-positive organisms compared with the strongly basic guanidines and quaternary bases, which were relatively stronger against Gram-negative organisms.

The amines prepared by us were selected in order to compare the activities of primary, secondary, and tertiary amines and study the effect of varying the chain length and position of the amino-group in the chain.

Five unbranched primary amines were made, two with a terminal amino-group, one with the amino-group near the end of the chain, and two with the amino-group in the centre of the chain. Unfortunately, attempts to prepare branched-chain primary amines were unsuccessful. Eight aliphatic secondary amines were made, all of which with two exceptions were unbranched. The chain lengths varied from 11 to 20 carbon atoms with the amino-group in the centre of the chain in four instances. In addition, a secondary amine containing a benzyl group was prepared, and five *N*-alkyl*cyclo*hexylamines. Twelve aliphatic tertiary amines with unbranched carbon chains consisting of from 13 to 30 carbon atoms were prepared. A tertiary amine containing a benzyl group was also prepared.

Three methods were used for the preparation of 8-*aminopentadecane*, but both Leuckart's method and reduction of diheptyl ketoxime gave poor yields. The most satisfactory method proved to be reductive amination of diheptyl ketone. Reductive amination was also employed for the preparation of 2-amino-octane and 9-aminoheptadecane. 1-Aminohexadecane was prepared by alkaline hydrolysis of *phthalocetylimide*, and 1-aminoheptadecane was prepared by Jeffrey's modification (*Amer. Chem. J.*, 1899, **22**, 31) of Hofmann's method (*Ber.*, 1882, **15**, 772).

It was our intention to make a series of branched-chain primary amines from dimethyldecylacetaldehyde, prepared by Darzens (*Compt. rend.*, 1932, **195**, 884) by condensation of acetone with ethyl α-chlorolaurate in presence of sodium ethoxide. From ethyl α-bromolaurate, however, none of the expected dimethyldecylacetaldehyde was obtained, but only undecanal, identified as its 2 : 4-dinitrophenylhydrazone. A similar result was obtained when *cyclo*hexanone was used in place of acetone.

Darzens and Levy (*Compt. rend.*, 1933, **196**, 184, 348) showed that α-bromo-acids react with sodium alkoxides to give α-alkoxy-acids and that these on distillation with copper yield aldehydes; they prepared undecanal in this way from α-methoxylauric acid. This is believed to explain the formation of undecanal in the above reaction, the bromine atom, in contrast to the chlorine atom, reacting preferentially with the ethoxy-group instead of with the ketone. Undecanal was reductively condensed with butylamine to give butylundecylamine. Di-*n*-octylamine and di-*n*-nonylamine were prepared by catalytic hydrogenation of the

appropriate nitriles, and the other secondary amines were obtained as by-products in the preparation of the tertiary amines.

With two exceptions, the tertiary amines were prepared by heating an alkyl bromide with ammonia or the appropriate primary amine under pressure, as described by Blicke and Zienty (*J. Amer. Chem. Soc.*, 1939, **61**, 771) and King and Work (*J.*, 1940, 1307; 1942, 401), secondary amines being obtained as by-products. For the preparation of methyldi-*n*-octylamine, this method was found superior to that described for the preparation of diallylamine (*Org. Synth.*, Coll. Vol. I, 195) in which the alkyl bromide is converted into the dialkylcyanamide by treatment with sodium cyanamide, hydrolysed to the dialkylamine with acid, and then alkylated. Methyl-*n*-hexyl-*n*-octylamine and *tri*-n-*nonylamine* were prepared from methyl-*n*-hexylamine and di-*n*-nonylamine respectively by reaction with the appropriate alkyl bromide.

Five alkyl *cyclo*hexylamines were prepared, four being obtained by the action of the corresponding alkyl bromide on *cyclo*hexylamine in presence of pyridine or sodium carbonate, and the fifth by catalytic hydrogenation of a mixture of *cyclo*hexanone and the alkylamine.

Although many of the amines formed crystalline hydrochlorides, some did not, and the long-chain tertiary amines were in general best characterised by means of their oxalates, which had sharp m. p.'s, whilst several of the primary and secondary amines formed beautifully crystalline salts with *m*-nitrobenzenesulphonic acid. So far as we are aware this acid has not previously been used for the characterisation of amines.

The antibacterial activities of the amines were tested against *Streptococcus hæmolyticus* and *Staphylococcus aureus* in a synthetic medium and in glucose broth by a method similar to that used by Fuller (*loc. cit.*). Most of the compounds were also tested against *Escherichia coli* but were relatively ineffective. The dilutions of the most active compounds necessary to inhibit the growth of the other two organisms are recorded in the table. It would appear from these and other results not reported in detail that the antibacterial activity of the aliphatic amines increases to a maximum with substances containing about 17—20 carbon atoms and then decreases. There was very little difference in the activities of secondary and tertiary amines containing the same number of carbon atoms. An insufficient number of compounds was available, however, to judge the effect of chain branching. Several of the compounds were inhibitory towards *Mycobacterium tuberculosis*; the results with this organism will be described elsewhere. Unfortunately, the most potent compounds *in vitro* had no effect *in vivo*, and it was shown that the amines on injection disappeared rapidly from the blood stream.

In view of recent attempts to correlate the biological and the physical properties of chemically related substances, it was considered of interest to compare the dissociation constants of certain of these amines with their antibacterial activities.

The dissociation constants of some simple aliphatic amines have been measured by Bredig (*Z. physikal. Chem.*, 1894, **13**, 297), using a conductivity procedure, and by Hall and Sprinkle (*J. Amer. Chem. Soc.*, 1932, **54**, 3469), using an electrometric titration method. We used the latter, which was more convenient and gave sufficiently accurate results for our purpose. Three series of amines were investigated: (*a*) dialkylamines containing between 4 and 18 carbon atoms; (*b*) trialkylamines containing between 6 and 27 carbon atoms; and (*c*) dioctylamine and alkyldioctylamines containing between 17 and 24 carbon atoms. The results are recorded in the tables together with the antibacterial activities. There would appear to be little or no correlation between dissociation constants and antibacterial activities in this particular series of compounds. All the amines tested proved to be relatively strong bases, whereas no marked antibacterial activity appeared until the number of carbon atoms exceeded 12.

Experimental.

Preparation of Amines.—*8-Aminopentadecane.* A mixture of diheptyl ketone (38 g.), ammonium carbonate (36 g.), and 85% formic acid (37 g.) was heated at 185—190° for 4 hours, and the reaction mixture poured into water. The resulting oil was extracted with ether and distilled, the fraction, b. p. 220—230°/15 mm., being collected; yield 16 g. This was redistilled, giving *formamidopentadecane* (Found: C, 75·1; H, 12·7; N, 5·2. $C_{16}H_{33}ON$ requires C, 75·3; H, 13·0; N, 5·5%). Hydrolysis of this compound was sluggish but was eventually accomplished by heating with anhydrous hydrogen chloride at 150°. The resulting oil formed a *m-nitrobenzenesulphonate*, fine needles, m. p. 150°, from benzene (Found: C, 59·1; H, 8·9; N, 6·4; S, 7·1. $C_{21}H_{38}N_2O_5S$ requires C, 58·6; H, 8·9; N, 6·5; S, 7·4%). 8-Aminopentadecane was also prepared in 5% yield by the reduction of diheptyl ketoxime (Kipping, *J.*, 1893, **63**, 454) with sodium and alcohol, according to the method of Thoms and Mannich (*Ber.*, 1903, **36**, 2554), but a much better method was reductive amination of diheptyl ketone. A mixture of the ketone (40 g.), ammonia (*d*, 0·880, 40 ml.), and ethyl alcohol (400 ml.) was hydrogenated at 72 atm. and 150° in presence of Raney nickel (5 g.). After the catalyst had been filtered off, the filtrate was acidified, filtered, and the filtrate made alkaline and extracted with ether. The oil remaining after removal of the ether was distilled, the 8-aminopentadecane distilling at 157°/12 mm.; yield 30·5 g. (56%).

9-Aminoheptadecane was prepared by reductive amination of dioctyl ketone (15 g.; prepared from the lead salt of pelargonic acid) in presence of Raney nickel as described for the preparation of 8-aminopentadecane. The catalyst was filtered off, and alcohol removed from the filtrate by distillation. *m*-Nitrobenzenesulphonic acid was added to the solution, and the precipitated *9-aminoheptadecane m-nitrobenzenesulphonate* was recrystallised from light petroleum (b. p. 60—80°), forming a micro-crystalline powder, m. p. 142—143° (12 g.) (Found: C, 60·4; H, 9·1; N, 5·7; S, 6·9. $C_{23}H_{42}O_5N_2S$ requires C, 60·3; H, 9·2; N, 6·1; S, 7·0%).

2-Amino-octane was prepared as described above by reductive amination of methyl *n*-hexyl ketone (64 g.). The amine was extracted with ether and distilled, the fraction, b. p. 164—166°, being collected (lit., b. p. 164°); yield 41 g.

1-*Aminohexadecane.* Cetyl iodide (28 g.) and potassium phthalimide (14·4 g.) were heated together for 4 hours, cooled, digested with water, and then extracted with ether. The extract was washed with sodium hydroxide solution and water, and the ether removed. On boiling the residue with alcohol, *phthalocetylimide* crystallised out; this was recrystallised from ethyl alcohol, m. p. 73—74° (25 g., 84%) (Found: C, 77·6; H, 10·3; N, 4·6. $C_{24}H_{37}O_2N$ requires C, 77·6; H, 10·0; N, 3·8%). The compound was resistant both to acid hydrolysis and to the hydrazine method of Ing and Manske (*J.*, 1926, 2348). On heating 10 g. with a mixture of 40% sodium hydroxide solution (100 ml.) and ethyl alcohol (120 ml.), however, 1-aminohexadecane was obtained (4·5 g.). This formed a hydrochloride, m. p. 140—145°, and a picrate, m. p. 75—78°.

1-*Aminoheptadecane.* Stearamide (28·7 g.), prepared from stearic acid *via* the acid chloride, was dissolved in methyl alcohol (250 ml.), and a solution of sodium (4·6 g.) in methyl alcohol (143 ml.) added to the warm solution, followed by bromine (16 g.) drop by drop with shaking. After addition of all the bromine, the mixture was warmed on the steam-bath for 10 mins. and allowed to stand. The mixture of unchanged stearamide and *N*-*n*-heptadecyl-*N'*-stearylurea was filtered off, and the filtrate diluted with water. The precipitated stearylurethane, recrystallised from ethyl alcohol, had m. p. 70—75°. A solution of the crude urethane (5 g.) in 10% aqueous alcoholic sodium hydroxide was heated under reflux for 16 hours, and the reaction mixture extracted with ether. The oil left after removal of the ether solidified, m. p. *ca.* 40°, and was converted into 1-aminoheptadecane hydrochloride, m. p. 162—164° (lit., 158°), by dissolving the base in ether and passing in dry hydrogen chloride (Found: N, 5·0; Cl, 12·0. Calc. for $C_{17}H_{38}NCl$: N, 4·8; Cl, 12·2%). The *acetyl* compound had m. p. 62° (Found: N, 5·0. $C_{19}H_{39}ON$ requires N, 4·7%). The recovered *N*-*n*-heptadecyl-*N'*-stearylurea was freed from stearamide by extraction with methanol, and the crude urea, m. p. 104—105°, fused with potassium hydroxide, as described by Hofmann (*loc. cit.*). A further crop of 1-aminoheptadecane was thereby obtained.

2-*Octylamino-octane.* A mixture of 2-amino-octane (41 g.), octyl bromide (62 g.), ethyl alcohol (250 ml.), and sodium carbonate (10 g.) was heated in an autoclave at 160° for 9 hours. The reaction mixture was acidified, the alcohol distilled off, and water added to the residue. The mixture was then made alkaline, extracted with ether, and the oil remaining after removal of the ether distilled. The 2-octylamino-octane distilled at 165°/14 mm. It formed a *hydrochloride* as a microcrystalline powder, m. p. 151—152° from acetone (Found: N, 5·1; Cl, 12·4. $C_{16}H_{36}NCl$ requires N, 5·0; Cl, 12·8%), and a *m-nitrobenzenesulphonate* as iridescent prisms, m. p. 75—76° from light petroleum (Found: C, 59·0; H, 8·8; N, 6·6; S, 7·7. $C_{22}H_{40}N_2O_5S$ requires C, 59·5; H, 9·0; N, 6·3; S, 7·2%).

Hexadecylethylamine was prepared from ethylamine hydrochloride (24 g.), sodium hydroxide, and cetyl iodide (55 g.) by the method used for 2-octylamino-octane. It had b. p. 210°/15 mm. and formed a *hydrochloride*, m. p. 206—207° (from ethyl alcohol) (Found: C, 70·9; H, 12·8; N, 4·5; Cl, 11·0. $C_{18}H_{40}NCl$ requires C, 70·7; H, 13·1; N, 4·6; Cl, 11·6%).

Butylundecylamine. An attempt to prepare α*α*-dimethyldecylacetaldehyde by Darzens's method (*loc. cit.*) was unsuccessful. A solution of ethyl α-bromolaurate (154 g.; prepared by bromination of lauryl chloride, followed by esterification) in dry acetone (30 g.) and dry ether (150 ml.) was cooled to − 10°, sodium ethoxide (made by dissolving 12·5 g. of sodium in dry ethyl alcohol and evaporation to dryness) added, and the mixture left with occasional shaking for 24 hours; sodium bromide separated out. Dilute acetic acid was then added, and the solution extracted with ether. The residue left after removal of the ether was distilled, the fraction, b. p. 165—170°/5 mm., being collected (71 g.). The redistilled aldehyde gave a 2 : 4-dinitrophenylhydrazone, m. p. 102°, which was shown by analysis to be *undecanal 2 : 4-dinitrophenylhydrazone* (Found: C, 57·8; H, 7·4; N, 16·0. $C_{17}H_{26}O_4N_4$ requires C, 58·3; H, 7·4; N, 16·0%). A mixture of undecanal and *n*-butylamine was hydrogenated in presence of Raney nickel as described for 2-octylamino-octane, giving butylundecylamine, characterised as its *m-nitrobenzenesulphonate*, m. p. 92—94° (Found: C, 58·2; H, 8·8; N, 6·6. $C_{21}H_{38}N_2O_5S$ requires C, 58·6; H, 8·8; N, 6·5%). Undecanal was also obtained when ethyl α-bromolaurate was treated with *cyclo*hexanone and sodium ethoxide.

Di-*n*-hexylamine, b. p. 125—130°/16 mm., was obtained as a by-product from the preparation of tri-*n*-hexylamine (*q.v.*). It yielded a *m-nitrobenzenesulphonate*, m. p. 119—120° (Found: C, 55·8; H, 8·3; N, 7·1; S, 8·2. $C_{18}H_{32}O_5N_2S$ requires C, 55·7; H, 8·25; N, 7·2; S, 8·25%).

Di-*n*-octylamine was prepared by hydrogenating a solution of octoic nitrile (40 g.) in ethyl alcohol (300 ml.) at 75 atm. and 80° in presence of Raney nickel (3 g.). The oil remaining after removal of the alcohol was distilled, di-*n*-octylamine distilling at 178°/15 mm. (yield 16 g., 45%), together with *n*-octylamine. Di-*n*-octylamine was also obtained as a by-product in the preparation of tri-*n*-octylamine. It formed a hydrochloride, m. p. 238°, and a *m-nitrobenzenesulphonate*, m. p. 115—116° (Found: C, 60·3; H, 9·3; N, 6·1. $C_{22}H_{40}N_2O_5S$ requires C, 59·5; H, 9·6; N, 6·3%).

Di-*n*-nonylamine was similarly prepared by hydrogenation of a solution of nonoic nitrile (44 g.) in alcohol (270 ml.) at 78 atm. and 65° in presence of Raney nickel (cf. Mailhe, *Bull. Soc. chim.*, 1918, **23**, 235). After removal of the alcohol, the residue was distilled, di-*n*-nonylamine boiling at 188°/12 mm. (23 g., 66%) (Found: C, 80·0; H, 14·3; N, 5·1. Calc. for $C_{18}H_{39}N$: C, 80·3; H, 14·5; N, 5·2%). In moist air it solidified to a *monohydrate*, which melted at 42°, passed through a mesomorphic smectic phase, and gave a clear stable liquid phase at 52° (Found: C, 75·8; H, 14·1; N, 5·0. $C_{18}H_{39}N,H_2O$ requires C, 75·3; H, 14·3; N, 4·9%). Mailhe (*loc. cit.*) gives m. p. 29°. It formed a *m-nitrobenzene-*

sulphonate which crystallised in waxy platelets, m. p. 107—108°, from light petroleum (Found: C, 61·3; H, 9·3; N, 5·6; S, 7·2. $C_{24}H_{44}N_2O_5S$ requires C, 61·0; H, 9·3; N, 5·9; S, 6·8%), and a hydrochloride, m. p. 230—232°, from *cyclo*hexane–dioxan. Di-*n*-nonylamine (13 g.) was also prepared by refluxing *n*-nonylamine (30 g.) with Raney nickel (3 g.) for 3 hours.

Di-*n*-decylamine was prepared by heating decyl bromide with ammonia (*d*, 0·880) in an autoclave. The appropriate fraction solidified on standing, m. p. 44—49° (lit., 47·5°). It formed a *hydrochloride*, m. p. 208—210°, from acetone (Found: C, 72·9; H, 12·7; N, 4·3; Cl, 9·3. $C_{20}H_{44}NCl$ requires C, 72·0; H, 13·2; N, 4·2; Cl, 10·7%).

*iso*Amyl-*n*-hexylamine was obtained as the main product in the preparation of *iso*amyldi-*n*-hexylamine (*q.v.*). It had b. p. 100—105°/22 mm. and formed a hydrobromide, m. p. 247—250°, and an *oxalate*, m. p. 219—220° (Found: C, 59·2; H, 9·9; N, 4·9. $C_{13}H_{27}O_4N$ requires C, 59·8; H, 10·3; N, 5·4%).

Benyl-*n*-hexylamine was obtained as a by-product in the preparation of benzyldi-*n*-hexylamine (*q.v.*). It had b. p. 128—130°/12 mm. and formed a *hydrobromide*, m. p. 217—218° from benzene (Found: C, 57·2; H, 8·0; N, 4·8; Br, 29·4. $C_{13}H_{22}NBr$ requires C, 57·3; H, 8·1; N, 5·1; Br, 29·4%).

Methyl-di-*n*-hexylamine was prepared from *n*-hexyl bromide and methylamine by the method of Blicke and Zienty (*loc. cit.*). It had b. p. 121—122°/19 mm. and formed a hydrochloride, m. p. 144—145° (Found: N, 5·6. Calc. for $C_{13}H_{30}NCl$: N, 5·9%). *iso*Amyldi-*n*-hexylamine was prepared in a similar manner from *n*-hexyl bromide (85 g.) and *iso*amylamine (20 g.). The product was distilled, the fraction, b. p. 100—105°/22 mm. (16 g.), yielding *iso*amyl-*n*-hexylamine (*q.v.*), and the fraction, b. p. 140—145°/22 mm. (3 g.), *iso*amyldi-*n*-hexylamine. This gave an *oxalate*, m. p. 128—130° (Found: C, 65·6; H, 10·9; N, 4·2. $C_{19}H_{39}O_4N$ requires C, 66·1; H, 11·3; N, 4·1%). Tri-*n*-hexylamine was prepared in a similar manner from *n*-hexyl bromide (100 g.) and alcoholic ammonia. The product was distilled, the fraction, b. p. 125—130°/16 mm. (10 g.), yielding di-*n*-hexylamine (*q.v.*), and the fraction, b. p. 165—170°/16 mm. (15 g.), yielding tri-*n*-hexylamine. The latter gave an *oxalate*, m. p. 120° (from water) (Found: C, 66·8; H, 11·4; N, 4·0. $C_{20}H_{41}O_4N$ requires C, 66·8; H, 11·4; N, 3·9%). It also formed an oily hydrochloride and a crystalline *m*-nitrobenzenesulphonate, m. p. 107—108°.

Benzyldi-*n*-hexylamine was prepared from benzylamine (20 g.) and hexyl bromide (62 g.) by the method of King and Work (*J.*, 1940, 1307). The product was distilled, the fraction, b. p. 128—130°/12 mm. (17 g.), yielding benzyl-*n*-hexylamine (*q.v.*), and the fraction, b. p. 185—195°/30 mm. (15 g.), yielding benzyldi-*n*-hexylamine. The latter formed a micro-crystalline *oxalate*, m. p. 95° (from benzene) (Found: C, 68·3; H, 9·2; N, 3·5. $C_{21}H_{35}O_4N$ requires C, 69·0; H, 9·6; N, 3·8%).

Methyl-*n*-hexyl-*n*-octylamine was prepared by heating methyl-*n*-octylamine (17 g.; obtained as a by-product in the preparation of methyldi-*n*-octylamine) with *n*-hexyl bromide (25 g.) in benzene (150 ml.) at 160° for 7 hours. The benzene was distilled off, and the residue made alkaline and extracted with light petroleum. The tertiary amine distilled at 140—145°/22 mm. It formed a microcrystalline *oxalate*, m. p. 227—228° (decomp.), when crystallised from aqueous alcohol (Found: C, 64·3; H, 10·8; N, 4·7. $C_{17}H_{35}O_4N$ requires C, 64·3; H, 11·0; N, 4·4%).

Methyldi-*n*-octylamine was best prepared by the method of Blicke and Zienty (*loc. cit.*) from *n*-octyl bromide (250 g.; 2 mols.) and 30% methylamine solution (200 ml.; 3 mols.) by heating for 10 hours at 165°. The mixture was made alkaline and extracted with light petroleum. The oil remaining after removal of the ether was distilled, the fraction, b. p. 140—160°/15 mm. (5 g.), consisting of methyl-*n*-octylamine, and that of b. p. 162—165°/15 mm. or 158°/10 mm. (6·8 g.; 42%) of methyldi-*n*-octylamine, and that boiling above this range largely of tri-*n*-octylamine. Methyldi-*n*-octylamine is stated by Blicke and Zienty (*loc. cit.*) to boil at 136—138°/5 mm., and by Westphal and Jerchel (*Ber.*, 1940, **73**, 1002) at 143—145°/3 mm. Methyldi-*n*-octylamine hydrochloride, m. p. 149—150° (lit. 149—150°), was prepared by passing dry hydrogen chloride into a solution of the amine in light petroleum.

Ethyldi-n-*octylamine*, prepared by a similar method from *n*-octyl bromide and ethylamine, had b. p. 166—167°/10 mm. (Found: C, 80·1; H, 14·4; N, 4·7. $C_{18}H_{39}N$ requires C, 80·3; H, 14·5; N, 5·2%). n-*Propyldi*-n-*octylamine* was similarly prepared from *n*-octyl bromide and *n*-propylamine; it had b. p. 174°/10 mm. (Found: C, 80·7; H, 13·7; N, 5·1. $C_{19}H_{41}N$ requires C, 80·6; H, 14·5; N, 5·0%). Tri-*n*-octylamine was similarly prepared from *n*-octyl bromide (130 g.) and ammonia (*d*, 0·880; 150 ml.). On distillation of the product, the fraction of b. p. 190—195°/16 mm. yielded di-*n*-octylamine (10 g.) (*q.v.*), and that of b. p. 225—230°/16 mm. tri-*n*-octylamine (30 g.). The latter, purified by redistillation, had b. p. 212—218°/12 mm. or 164—168°/0·7 mm. (Found: C, 82·3; H, 13·7; N, 4·3. Calc. for $C_{24}H_{51}N$: C, 81·6; H, 14·4; N, 4·0%).

Methyldi-*n*-nonylamine was prepared by a similar method to that used by King and Work (*J.*, 1942, 401) from *n*-nonyl bromide and methylamine. It had b. p. 204°/25 mm. and formed a micro-crystalline *hydrochloride*, m. p. 149—150°, from benzene (Found: C, 71·6; H, 13·0; N, 4·6; Cl, 11·2. $C_{19}H_{42}NCl$ requires C, 71·3; H, 13·1; N, 4·4; Cl, 11·1%). *Ethyldi*-n-*nonylamine* was similarly prepared from *n*-nonyl bromide and ethylamine. It had b. p. 208°/20 mm. and formed a micro-crystalline *hydrochloride*, m. p. 78—79°, from light petroleum (Found: C, 71·9; H, 12·8; N, 4·6; Cl, 10·1. $C_{20}H_{44}NCl$ requires C, 72·0; H, 13·2; N, 4·2; Cl, 10·61%).

Tri-n-*nonylamine* was prepared by heating di-*n*-nonylamine (7 g.), *n*-nonyl bromide (20 g.), anhydrous sodium carbonate (10 g.), and ethyl alcohol (200 ml.) at 160° for 9 hours with stirring. The reaction mixture was filtered, the filtrate acidified to Congo-red with dry hydrogen chloride, and again filtered, and the solvent removed. The residue was made alkaline with sodium hydroxide and extracted with ether. The extract was evaporated and the residue distilled in a vacuum, tri-*n*-nonylamine distilling at 178—180°/0·01 mm.; yield 5 g. (49%) (Found: C, 81·8; H, 14·6; N, 3·53. $C_{27}H_{57}N$ requires C, 82·0; H, 14·5; N, 3·54%). It formed a microcrystalline *oxalate*, m. p. 107—108°, from dioxan (Found: C, 71·8; H, 11·8; N, 3·35. $C_{29}H_{59}O_4N$ requires C, 71·7; H, 12·2; N, 2·9%).

Tri-*n*-dodecylamine was prepared from *n*-dodecyl iodide (82 g.) and ammonia (*d* 0·880; 300 ml.) by the method described above. The product was distilled in a vacuum, the fraction, b. p. 290—310°/15 mm., (13 g.) consisting mainly of di-*n*-dodecylamine. The residue (25 g.), which would not distil at 15 mm. pressure, was converted into the hydrochloride by passing dry hydrogen chloride into a light

petroleum solution; this had m. p. 78—79° (lit. 78—79°) (Found: C, 77·5; H, 13·4; N, 2·6; Cl, 6·1. Calc. for $C_{36}H_{76}NCl$: C, 77·5; H, 13·6; N, 2·5; Cl, 6·3%).

cyclo*Hexyl*-n-*hexylamine*. *cyclo*Hexylamine (22 g.), *n*-hexyl bromide (73·5 g.), sodium carbonate (10 g.), and alcohol (250 ml.) were heated together at 160° for 6 hours and worked up as previously described. The product was distilled in a vacuum, the fraction of b. p. 125—135°/15 mm. (16 g.) being collected. By passing dry hydrogen chloride into a light petroleum solution of the amine, this was converted into cyclo*hexyl*-n-*hexylamine hydrochloride*, m. p. 240°, after recrystallisation from water (Found: C, 65·1; H, 11·8; N, 6·9; Cl, 16·1. $C_{12}H_{26}NCl$ requires C, 65·6; H, 11·8; N, 6·4; Cl, 16·2%).

*cyclo*Hexyl-*n*-octylamine was prepared by heating a mixture of *cyclo*hexylamine (38 g.) and *n*-octyl bromide (74 g.) with pyridine (80 ml.) under reflux for 4½ hours. The reaction mixture was poured into water, made alkaline with sodium hydroxide, and extracted with light petroleum. The residue remaining after removal of the petroleum was distilled, the secondary amine distilling at 145—150°/13 mm. (38 g.). It gave a *hydrochloride*, m. p. 212°, which formed a micro-crystalline powder from acetonitrile (Found: C, 68·0; H, 12·1; N, 5·6; Cl, 14·2. $C_{14}H_{30}NCl$ requires C, 67·9; H, 12·1; N, 5·7; Cl, 14·3%) and platelets from dioxan (Found: C, 67·9; H, 11·9; N, 5·5%).

*cyclo*Hexyl-*n*-nonylamine was prepared by hydrogenating a solution of *cyclo*hexanone (14·3 g.) and *n*-nonylamine (21 g.) in alcohol (175 ml.) at 100 atm. and 140° in presence of Raney nickel (5 g.). The compound was isolated in the usual way, b. p. 160°/12 mm.; yield 17 g. It formed a *hydrochloride*, m. p. 216°, which crystallised from acetone–light petroleum as a flocculent powder (Found: C, 68·8; H, 12·5; N, 5·5; Cl, 13·9. $C_{15}H_{32}NCl$ requires C, 68·8; H, 12·2; N, 5·4; Cl, 13·6%).

*cyclo*Hexyl-*n*-decylamine was prepared from *cyclo*hexylamine (26 g.), *n*-decyl bromide (50 g.), and pyridine (50 ml.) as described for the octyl compound. It had b. p. 155—160°/16 mm. and formed a *hydrobromide*, m. p. 228—230°, which crystallised from acetone in fine needles (Found: C, 60·6; H, 10·2; N, 4·4; Br, 25·0. $C_{16}H_{34}NBr$ requires C, 60·0; H, 10·6; N, 4·4; Br, 25·0%). *cyclo*Hexyl-*n*-dodecylamine was prepared in a similar manner from *cyclo*hexylamine (32 g.), *n*-dodecyl iodide (96 g.), and pyridine (80 g.). It had b. p. 200—205°/15 mm.; yield 24 g. (28%). It formed a hydrochloride, m. p. 202°, which crystallised from acetone (lit., 204—205°) (Found: C, 71·1; H, 12·3; N, 4·8; Cl, 11·3. Calc. for $C_{18}H_{38}NCl$: C, 71·2; H, 12·5; N, 4·6; Cl, 11·7%).

Dissociation Constants.—A standard sealed glass–saturated calomel electrode system was used, in conjunction with a Cambridge bench pH meter, for most of the electrometric titrations. For pH measurements of strongly alkaline solutions, however, the standard sealed glass electrode was replaced by a special " Alki " electrode, which permits accurate measurements in the pH range 9·0—14·0. All measurements were performed in a water thermostat at 25°. During the titrations, the solution was agitated by passing through it nitrogen which had previously been bubbled through a flask containing 70% aqueous alcohol at 25°.

Dissociation Constants and Bacteriostatic Activities.

Amine.	B. p.	pK_a in 70% alcohol.	Bacteriostatic activity × 10^{-3}. Synthetic medium. Staph. aureus No. 663.	Synthetic medium. Strep. No. 618.	Glucose broth. Staph. aureus No. 663.	Glucose broth. Strep. No. 618.
(1) *Secondary amines.*						
*Diethylamine	55—56°	9·78	50	5	5	5
*Dipropylamine	110	9·47	5	5	5	5
*Dibutylamine	159—160	9·57	1	5	1	1
*Diamylamine	202—204	9·53	5	1	1	1
Dihexylamine	112—114/12 mm.	9·33	5	10	1	5
Dioctylamine	164/12 mm.	9·20	50	100	100	100
Dinonylamine	188/12 mm.	9·29	50	100	100	500
(2) *Tertiary amines.*						
*Triethylamine	89—90	9·25	5	5	1	5
*Tripropylamine	156	9·0	5	1	1	1
*Tributylamine	209—214	8·92	5	5	1	1
*Triamylamine	127/11 mm.	8·79	5	5	5	5
Trihexylamine	150—159/12 mm.	8·53	5	10	5	5
Trioctylamine	164—168/0·7 mm.	8·35	50	50	10	10
Trinonylamine	178—180/0·01 mm.	8·21	50	50	10	10
(3) *Dioctyl- and alkyldioctyl-amines.*						
Dioctylamine	164/12 mm.	9·20	50	100	100	100
Methyldioctylamine	158/10 mm.	8·56	500	500	100	500
Ethyldioctylamine	166—167/10 mm.	8·70	100	100	100	100
Propyldioctylamine	174/10 mm.	8·51	100	100	10	50
Trioctylamine	164—168/0·7 mm.	8·35	50	50	10	10

* Prepared from commercial specimens.

All the amines were examined in 70% aqueous alcoholic solution. This was the minimum concentration of alcohol at which a 0·002M-solution of the least soluble amine (*i.e.*, trinonylamine) could be prepared. The alcohol used for preparing the solutions was freshly distilled. Conductivity water (supplied by Mr. James, of Battersea Polytechnic) was used for some of the experiments; this did

not offer any advantages over freshly redistilled water, which was therefore used in the other experiments. Blank titrations were performed on each sample of alcohol and redistilled water to ensure that they were suitable. All the amines were freshly purified by redistillation.

It is well known that alcohol depresses the dissociation constants of acids (cf. Hall and Sprinkle, *loc. cit.*), and in order to compare our results with previously published data, we measured some of the simpler amines in aqueous solution. These results were in good agreement with published data.

Each of the dissociation constants recorded in the tables is the mean of six determinations.

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48. *Preparation of Iodinated Mono- and Di-phenyl-acetic and -propionic Acids.*

By JEAN W. BARNETT, F. A. ROBINSON, and BARBARA M. WILSON.

The preparation of nine iodinated *derivatives* of mono- and di-phenyl-acetic and -propionic acids is described.

3 : 5-*Di-iodo-* and **3 : 4 : 5-*tri-iodo-phenylacetic acid*** were prepared from **3 : 5-*di-iodo*-4-*amino*-*phenylacetic acid.*** This was obtained by iodination of *p*-aminophenylacetic acid (*Org. Synth.*, Coll. Vol. I, 44) by a method analogous to that used for the preparation of 3 : 5-di-iodo-4-aminobenzoic acid by Wheeler and Liddle (*Amer. Chem. J.*, 1920, **42**, 456). Replacement of the amino-group of 3 : 5-di-iodo-4-aminophenylacetic acid by hydrogen proved unexpectedly difficult, the usual methods yielding black tars. Satisfactory results were eventually obtained by adding a solution of the diazonium salt to a cold alcoholic suspension of cuprous oxide (cf. Hodgson and Turner, *J.*, 1942, 748). The amino-group was readily replaced by iodine by the standard method.

3 : 5-*Di-iodo*-2-*hydroxyphenylacetic acid* was prepared by iodination of *o*-hydroxyphenylacetic acid with iodine in potassium iodide.

3 : 5-*Di-iodo*-4-*hydroxydiphenylacetic acid* was prepared by iodination of *p*-hydroxydiphenylacetic acid, obtained by the method of Bistrzycki and Flatau (*Ber.*, 1895, **28**, 987). This method gave unsatisfactory results unless very pure mandelic acid was used as the starting material. Even then, crystallisation was very slow.

3 : 5-*Di-iodo*-2-*hydroxydiphenylacetic acid* was prepared by iodination of *o*-hydroxydiphenylacetic acid, which is known in the form of its lactone, 3-phenyl*iso*coumaranone (Bistrzycki, *Ber.*, 1897, **30**, 124). This was converted into the acid by heating with sodium hydroxide and then iodinated by treatment with iodine in potassium iodide solution. Attempts to convert the resulting acid into the corresponding di-iodo*iso*coumaranone were unsuccessful.

α-*Phenyl*-β-3 : 5-*di-iodophenyl*- and **α-*phenyl*-β-3 : 4 : 5-*tri-iodophenyl-propionic acid*** were obtained from **α-*phenyl*-β-(3 : 5-*di-iodo*-4-*aminophenyl*)*propionic acid*** by methods analogous to those used in the preparation of the iodo-phenylacetic acids. Iodination of α-phenyl-β-*p*-aminophenylpropionic acid with 4 moles of iodine monochloride gave α-phenyl-β-(3 : 5-di-iodo-4-aminophenyl)propionic acid, but with 2 moles of iodine monochloride the product was mainly the mono-iodo-derivative.

α-Phenyl-β-(3 : 5-di-iodo-2-hydroxyphenyl)propionic acid was obtained as follows. Catalytic hydrogenation of 3-phenylcoumarin with Raney nickel gave 3-phenyl-3 : 4-dihydrocoumarin; this was described by Späth and Galinovsky (*Ber.*, 1937, **70**, 235), but the method of preparation was not disclosed. The coumarin was converted into the hydroxy-acid, and iodinated in potassium iodide solution. The resulting acid was converted into **6 : 8-*di-iodo*-3-*phenyl*-3 : 4-*dihydrocoumarin*** by heating at the melting point in a high vacuum.

α-*Phenyl*-β-(3 : 5-*di-iodo*-4-*hydroxyphenyl*)*ethane* was prepared from α-phenyl-β-*p*-hydroxyphenylethane, obtained as a product of the reduction of α-phenyl-β-*p*-hydroxyphenylacrylonitrile by means of sodium amalgam. α-Phenyl-β-*p*-methoxyphenylethane had previously been prepared by a similar method from α-phenyl-β-*p*-methoxyphenylacrylonitrile (Freund and Remse, *Ber.*, 1890, **23**, 2859), and the hydroxy-derivative prepared from it by demethylation (*Ber.*, 1901, **34**, 3081). The direct preparation of α-phenyl-β-*p*-hydroxyphenylethane from α-phenyl-β-*p*-hydroxyphenylacrylonitrile has not, however, been previously described.

Experimental.

All the iodo-compounds described below melted with decomposition.

3 : 4 : 5-*Tri-iodophenylacetic Acid.*—*p*-Aminophenylacetic acid (10·5 g.) was dissolved in excess of dilute hydrochloric acid and exactly two equivalents of iodine monochloride were added with shaking. A brown precipitate formed after 16 hours and was filtered off; m. p. 205—206°. Yield, 16·4 g. (58%). After recrystallisation from a large volume of boiling acetone and then from pyridine, **3 : 5-*di-iodo*-4-*aminophenylacetic acid*** was obtained in colourless needles, m. p. 220—221°; the m. p. was unchanged after further recrystallisation from pyridine (Found : C, 24·9; H, 1·80; N, 3·58; I, 65·0. $C_8H_7O_2NI_2$ requires C, 23·8; H, 1·74; N, 3·47; I, 63·0%). The compound was sparingly soluble in acetone, practically insoluble in alcohol and in ether.

3 : 5-Di-iodo-4-aminophenylacetic acid (3·5 g.) was diazotised by addition of solid sodium nitrite to an ice-cold solution in concentrated sulphuric acid. After 2 hours at 0°, the dark solution was poured on ice, and potassium iodide solution (9 g. in 20 ml. of water) added, giving a brown precipitate. The mixture was heated on the water-bath until no more nitrogen was evolved (about 1 hour). The product was then poured into saturated sodium hydrogen sulphite solution and the precipitated **3 : 4 : 5-*tri-iodophenylacetic acid*** was filtered off, washed with water, and recrystallised from acetone; m. p. 219—220°. Yield, 3·5 g. (78%). After two recrystallisations from acetone, the product was obtained in pale yellow needles, m. p. 224—225°, readily soluble in ether, in alcohol, and in acetone, but insoluble in water (Found : C, 18·9; H, 0·99; I, 74·6. $C_8H_6O_2I_3$ requires C, 18·7; H, 0·97; I, 74·1%).

3 : 5-*Di-iodophenylacetic Acid.*—3 : 5-Di-iodo-4-aminophenylacetic acid (3·5 g.) was diazotised as described above. After 2 hours at 0°, the solution of the diazonium salt was poured on ice and the clear ice-cold solution was added to a suspension of cuprous oxide (2 g.) in cold alcohol (150 ml.). Immediate evolution of nitrogen took place and, when this had slackened, the mixture was refluxed until no more nitrogen was given off (½ hour). The product was poured into one volume of water, and after 16 hours the precipitate was filtered off (together with cuprous oxide) and extracted with ether, in which the precipitate was readily soluble (the starting material was insoluble in ether). The ethereal extracts were washed with sodium thiosulphate solution and then with water, dried (Na_2SO_4), and evaporated to dryness. The residue was crystallised from boiling absolute alcohol and then from toluene. It formed pale yellow needles, m. p. 195—196°. Further recrystallisation from toluene caused no change in m. p. (Found : C, 25·0; H, 1·76. $C_8H_6O_2I_2$ requires C, 24·7; H, 1·55%). The *compound* was readily soluble in alcohol, in ether, and in boiling toluene, but insoluble in light petroleum and in water.

3 : 5-*Di-iodo*-2-*hydroxyphenylacetic Acid.*—Iodination of *o*-hydroxyphenylacetic acid (6 g.) dissolved in excess of N-sodium hydroxide solution, by addition with stirring of 2½ equivalents of iodine in 25% aqueous potassium iodide solution, gave a dark solution, from which the crude **3 : 5-di-iodo-2-hydroxyphenylacetic acid** was precipitated by pouring into sodium hydrogen sulphite solution. This precipitate was extracted twice with ether, and the extracts were washed once with water, dried (Na_2SO_4), and evaporated to a small bulk; **3 : 5-*di-iodo*-2-*hydroxyphenylacetic acid*** then crystallised as needles, m. p. 163—164°. Yield, 6·5 g. (41%). It was recrystallised from absolute alcohol; m. p. 164—165° (Found : C, 23·8; H, 1·67; I, 63·4. $C_8H_6O_3I_2$ requires C, 23·8; H, 1·49; I, 62·8%). The compound was readily soluble in alcohol and in ether but insoluble in light petroleum and in water.

3 : 5-*Di-iodo*-4-*hydroxydiphenylacetic Acid.*—*p*-Hydroxydiphenylacetic acid (5 g.) was dissolved in N-sodium hydroxide (100 ml.) and iodinated by addition of 2½ equivalents of iodine in 25% potassium iodide solution (150 ml.) with stirring. After ½ hour, it was worked up as described for the preparation of **3 : 5-di-iodo-2-hydroxyphenylacetic acid**. The residue was crystallised from boiling toluene, yielding 5 g. of **3 : 5-*di-iodo*-4-*hydroxydiphenylacetic acid*** as a micro-crystalline powder, m. p. 192°. The mother liquors gave a further 2·1 g., m. p. 190°. Total yield, 67%. Two further recrystallisations of the first crop from toluene gave crystals, m. p. 193—194° (Found : I, 52·5. $C_{14}H_{10}O_3I_2$ requires I, 52·9%). The substance was readily soluble in alcohol, in ether, and in boiling toluene, but insoluble in light petroleum and in water.

3 : 5-*Di-iodo*-2-*hydroxydiphenylacetic Acid.*—3-Phenyl*iso*coumaranone (19 g.) was iodinated in the manner described above by means of iodine in potassium iodide solution, the only difference being that the lactone could be dissolved in sodium hydroxide solution only by warming gently. After being worked up in the usual manner, the residue was crystallised from ether by cautious addition of light petroleum until just cloudy. **3 : 5-*Di-iodo*-2-*hydroxydiphenylacetic acid*** separated as a micro-crystalline powder, m. p. 142° (decomp.). Yield, 13·1 g. (33%). For analysis, it was recrystallised from ether–light petroleum, with no change of m. p. (Found : I, 52·7, 52·9. $C_{14}H_{10}O_3I_2$ requires I, 52·9%. $C_{14}H_8O_2I_2$ requires I, 55·0%). The compound was readily soluble in ether and in alcohol, but insoluble in light petroleum and in water.

An attempt to dehydrate the di-iodo-derivative by heating it gradually at 0·002 mm. up to 150° led to complete decomposition, only a deep-violet oil being obtained.

***α*-Phenyl-*β*-(3 : 5-*di-iodo*-4-*hydroxyphenyl*)*ethane.*—*α*-**Phenyl-*β*-*p*-hydroxyphenylacrylonitrile (10 g.) was dissolved in absolute alcohol (200 ml.) and reduced by slow addition of small lumps of sodium (23·3 g.) over a period of ½ hour, followed by prolonged heating on the water-bath until all the sodium had dissolved (*ca.* 4½ hours). After addition of one volume of water, the solution was concentrated under reduced pressure to small bulk. The residue was extracted thrice with ether, and the extracts were washed twice with dilute hydrochloric acid in order to remove the *β*-phenyl-*γ*-*p*-hydroxyphenylpropylamine, formed as a by-product in the reduction. They were finally washed once with water, dried, and evaporated under reduced pressure. The solid residue of *α*-phenyl-*β*-*p*-hydroxyphenylethane was recrystallised from aqueous alcohol, giving leaflets, m. p. 99—100° (lit., 100—101°). Yield, 4·7 g., together with a further 600 mg. of lower melting material (93—96°) from the mother liquors. Total yield, 67%.

To a solution of *α*-phenyl-*β*-*p*-hydroxyphenylethane (5 g.) in aqueous alcoholic ammonia [120 ml., made by adding 10 ml. of ammonia (*d*, 0·88) and 10 ml. of alcohol to 100 ml. of water], solid iodine (15 g.)

was added with mechanical stirring over a period of 15 minutes. A green solid separated from the solution almost immediately and increased in bulk on standing. The mixture was stirred for ½ hour, and the precipitate was then filtered off, dissolved in hot alcohol, and treated with charcoal; the filtrate was poured into water, whereby a sticky brown solid was precipitated. This was dissolved in ether, and the solution was dried (Na_2SO_4), and evaporated almost to dryness; the residue crystallised slowly; m. p. 80—81°. Yield, 4·5 g. (40%). The crude *α-phenyl-β-(3 : 5-di-iodo-4-hydroxyphenyl)ethane* was crystallised from ether–light petroleum; m. p. 82—83° (Found : C, 37·3; H, 2·60; I, 55·9. $C_{14}H_{12}OI_2$ requires C, 37·3; H, 2·67; I, 56·4%). The compound was readily soluble in ether and in alcohol, but insoluble in light petroleum and in water.

α-Phenyl-β-3 : 4 : 5-tri-iodophenylpropionic Acid.—α-Phenyl-β-*p*-aminophenylpropionic acid (5 g.) was dissolved in 2N-hydrochloric acid (1 l.) by warming on a water-bath and, after filtration from a trace of insoluble material, the cooled liquid was treated with iodine monochloride (15 g.; 4 mols.) in three portions, with continuous shaking during the addition. After 48 hours at 20°, the precipitate which had formed was filtered off and extracted thrice with ether. The extracts were washed in turn once with sodium thiosulphate solution which removed free iodine, and once with water, then dried (Na_2SO_4) and evaporated carefully almost to dryness. On standing, pure *α-phenyl-β-(3 : 5-di-iodo-4-amino-phenyl)propionic acid* crystallised in colourless prisms, m. p. 172—173°. Yield, 5·5 g. (53%). Recrystallisation from alcohol did not raise the m. p. (Found : C, 36·5; H, 2·64; N, 2·99; I, 51·5. $C_{15}H_{13}O_2NI_2$ requires C, 36·5; H, 2·64; N, 2·84; I, 51·3%). The compound was soluble in ether and in alcohol but insoluble in light petroleum.

α-Phenyl-β-(3 : 5-di-iodo-4-aminophenyl)propionic acid (3·5 g.) was dissolved in concentrated sulphuric acid (15 ml.) and diazotised by addition of solid sodium nitrite (1·85 g.) at 0°. After 15 minutes at 0°, it was poured on 3 vols. of ice, and filtered from a trace of insoluble material. To the ice-cold filtrate potassium iodide solution (11 g. in 20 ml. of water) was added, and the mixture warmed on the water-bath until no more nitrogen was given off and the oil had solidified forming a voluminous black precipitate. This was extracted thrice with ether, washed first with sodium thiosulphate solution to remove iodine, and then with water, dried (Na_2SO_4), and evaporated almost to dryness. *α-Phenyl-β-3 : 4 : 5-tri-iodophenylpropionic acid* crystallised at once from the concentrated ethereal solution as rectangular leaflets, m. p. 208—209°. Yield, 3·0 g. (70%). It was recrystallised from boiling absolute alcohol; m. p. 211—212°. A further recrystallisation did not raise the m. p. (Found : C, 30·2; H, 1·55; I, 63·0. $C_{15}H_{11}O_2I_3$ requires C, 29·8; H, 1·82; I, 63·1%).

α-Phenyl-β-3 : 5-di-iodophenylpropionic Acid.—α-Phenyl-β-(3 : 5-di-iodo-4-aminophenyl)propionic acid (3·5 g.) was diazotised and the solution of the diazonium salt treated with alcohol and cuprous oxide in the manner described for the preparation of 3 : 5-di-iodophenylacetic acid. The ethereal extract was evaporated to dryness and the residue taken up in toluene (3 ml.). Crystals of *α-phenyl-β-3 : 5-di-iodophenylpropionic acid*, m. p. 149—150°, were obtained. Yield, 1·25 g. (37%). Recrystallisation from toluene raised the m. p. to 153—154°, unchanged by a further recrystallisation (Found : C, 37·8; H, 2·70. $C_{15}H_{12}O_2I_2$ requires C, 37·5; H, 2·51%).

α-Phenyl-β-(3 : 5-di-iodo-2-hydroxyphenyl)propionic Acid.—3-Phenylcoumarin (5 g.) was refluxed with 10% sodium hydroxide solution (50 ml.) until completely dissolved and, after cooling to 20°, it was reduced catalytically with Raney nickel (prepared from 2 g. of alloy). Slightly more than the theoretical amount of hydrogen had been absorbed after 20 hours. The catalyst was filtered off, and the filtrate extracted once with ether. The alkaline solution was acidified and extracted thrice with ether, the extract washed with water, dried, and evaporated to small bulk. Crystallisation was best effected by allowing the concentrated ethereal solution to evaporate slowly at room temperature. When crystals had begun to form, light petroleum was added until a slight permanent cloudiness remained, yielding 3-phenyl-3 : 4-dihydrocoumarin, m. p. 115—116° (lit. 122°). Yield, 4·5 g. (89%).

3-Phenyl-3 : 4-dihydrocoumarin (14 g.) was dissolved in N-sodium hydroxide (250 ml.) by warming gently, and the solution treated with iodine (35 g.) in 10% aqueous potassium iodide solution (300 ml.). The mixture was stirred for ½ hour after the addition was completed, and the crude iodinated product precipitated by pouring into concentrated sodium hydrogen sulphite solution. The solid was filtered off, dissolved in ether, and the solution washed with water, dried, and evaporated almost to dryness. Careful addition of light petroleum yielded α-phenyl-β-(3 : 5-di-iodo-2-hydroxyphenyl)propionic acid, m. p. 130—132°. Yield, 14·0 g. (68%). Recrystallisation from toluene raised the m. p. to 141—142° (decomp.).

Attempted dehydration. When the above iodinated hydroxy-acid was heated gradually in an oil-bath to 140° at 0·005 mm., loss of water occurred when the melting point was reached. The temperature was maintained at *ca.* 145° for 15 minutes, and the mixture cooled and extracted with ether. Washing with sodium bicarbonate solution removed unchanged material. The remaining ethereal extract was washed with sodium thiosulphate solution and water, dried, and evaporated to dryness. The residue was crystallised from toluene, yielding 6 : 8-*di-iodo-3-phenyl-3 : 4-dihydrocoumarin*, m. p. 141—142° (no decomp.). Mixed m. p. with the original acid, 122—124°. It was insoluble in sodium bicarbonate and in cold sodium hydroxide solution, but dissolved in the latter after prolonged boiling (Found : C, 38·1; H, 2·12; I, 50·2. $C_{15}H_{10}O_2I_2$ requires C, 37·8; H, 2·10; I, 53·4%).

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49. *Epimeric Alcohols of the* cyclo*Hexane Series. Part VI. The Optically Active* 3-*Methyl*cyclo*hexanols.*

By A. Killen Macbeth and J. A. Mills.

The resolution of *dl-cis*-3-methyl*cyclo*hexanol is described, the *d*- and the *l*-form being characterised by a series of derivatives. The alkaloidal salts of the hydrogen phthalate of the *dl-trans*-alcohol give a separation of *l-trans*-3-methyl*cyclo*hexanol, but the isolation of the *d*-component was not satisfactorily achieved by the use of such salts. The use of *l*-menthylaminoacetic acid as a resolving agent has also been examined.

The preparation and characterisation of *dl-cis*- and *dl-trans*-3-methyl*cyclo*hexanols has already been described (*J.*, 1945, 709) and the resolution of the compounds has now been examined. The separation of the *dl-cis*-alcohol into its components is much easier than with the *dl-trans*-compound, for the hydrogen phthalate gives a reasonably stable series of salts with the common alkaloids, and of these the quinine salt may advantageously be used to give the initial separation of the *l*-component, and the strychnine salt may be used to obtain the pure *d*-component from the mother liquors. Although the cinchonidine salt of the *dl-cis*-hydrogen phthalate crystallises well, the physical properties of the *d*-, *l*-, and *dl*-compounds are so much alike that no appreciable resolution can be effected by the use of this salt. The best method of getting a good initial separation of the *l-cis*-quinine salt is to use the modification of Pickard's method (*J.*, 1907, **91**, 1973) in which half of the hydrogen phthalate is combined with the alkaloid and half with an alkali metal by the simultaneous use of quinine and sodium carbonate. Under these conditions the *l*-isomer separates as the quinine salt and the *d*-component mainly concentrates in the mother liquors which are used again thrice. The most satisfactory method for recovery of the *d*-component was found to be treatment with strychnine of the optically crude *d-cis*-hydrogen phthalate isolated from the mother liquors, and fractional crystallisation of the alkaloidal salt.

Clark and Read (*J.*, 1934, 1777) recorded the successful use of *l*-menthylaminoacetic acid in the resolution of *dl*-menthol, and this reagent gave with *dl-trans*-3-methyl*cyclo*hexanol a good yield of the ester as a non-crystallisable syrup which formed a solid sulphate. Repeated crystallisation of this salt ultimately yielded a small quantity of optically pure l-trans-3-*methyl*cyclo*hexyl* 1-*menthylaminoacetate*, but the yield of the ester was unpromisingly small and the attempted recovery of further solid from the mother liquors led to extensive decomposition. Other salts of the menthylglycine ester were tried with no better results, and we were unable to recover the pure *d*-component by this method.

Alkaloidal salts of the hydrogen phthalate of the *dl-trans*-alcohol were examined. Brucine, cinchonidine, and strychnine all gave well-defined salts, and of these the strychnine salts were found to be best for resolution work. On the addition of 70% of the theoretical amount of strychnine to *dl-trans*-3-methyl*cyclo*hexyl hydrogen phthalate in ethyl acetate the impure strychnine salt was mainly derived from the *l*-compound. Systematic fractional crystallisation from ethyl acetate gave a fair yield of the optically pure salt. As the melting point of the strychnine salt was not a good indication of optical purity and as the rotation of the salt was inconveniently low, the progress of the resolution was followed by occasional decomposition of the salt and examination of the isolated hydrogen phthalate. Some difficulty was at first experienced in getting a complete decomposition of the strychnine salt, but it was ultimately found satisfactory to form a concentrated solution in hot dioxan and run this into excess of dilute hydrochloric acid.

The hydrogen phthalate recovered from the mother liquors after the initial removal of the *l*-compound as the strychnine salt had a rotation which indicated some 70% of the *d*-component. No crystallisable alkaloidal salt, however, could be prepared of lower solubility than that derived from the *l*-ester which would have enabled the separation of the optically pure *d-trans*-compound to be effected.

Trial tests indicated that the phenylurethane might be used, and the crude *d*-hydrogen phthalate was hydrolysed to the alcohol and condensed with phenyl *iso*cyanate. Fractional crystallisation of the product gave a good yield of optically pure *d-trans*-3-methyl*cyclo*hexyl-phenylurethane. This constitutes a resolution of the alcohol, but is unsuitable inasmuch as the drastic conditions required for the hydrolysis of a phenylurethane do not lend themselves to the production of an optically pure alcohol.

When preparing derivatives of *l-cis*-3-methyl*cyclo*hexanol particular attention was paid to the phenylurethane and hydrogen phthalate to see if, like the *dl*-compounds, they were

dimorphic. Only one form of each could be isolated corresponding to the lower-melting of the *dl-cis*-derivatives.

Oxidation of the optically pure 3-methyl*cyclo*hexanols with chromic acid gave optically pure 3-methyl*cyclo*hexanones with rotations of the opposite sign: thus the *l-cis* and *l-trans*-alcohols gave the *d*-ketone, whereas the *d-cis*-alcohol gave *l*-3-methyl*cyclo*hexanone. Resolution of the *dl*-ketone with *l*-menthylhydrazide was described by Adams, Smith, and Loewe (*J. Amer. Chem. Soc.*, 1942, **64**, 2087), but their results show that it is a tedious and wasteful process. In view of this it would seem best to prepare the active forms of the ketone by the above oxidations when they are needed in quantity.

Experimental.

Resolution of dl-cis-3-*Methyl*cyclo*hexyl Hydrogen Phthalate.*—Both quinine and cinchonidine gave salts with the ester which could readily be recrystallised, but quinine proved to be the better alkaloid to use. The *dl*-ester (10 g.), anhydrous sodium carbonate (1·0 g.), and anhydrous quinine (6·2 g.) were dissolved in boiling aqueous alcohol (50%; 90 c.c.) and, after being seeded, the solution was allowed to cool slowly. After separation of the quinine salt (8·4 g.) the mother liquors were again used with *dl*-ester (11·7 g.), quinine (7·2), and sodium carbonate (1·2), and a further quantity (11·0 g.) of quinine salt was collected. A third lot of salt (4·1 g.) was prepared by the addition of *dl*-ester (5·0 g.) and equivalent quantities of alkaloid and sodium carbonate to the mother liquors. It was inadvisable to use the mother liquors more than thrice as the accumulation of the sodium salt made the separation of the quinine salt very slow. The combined quinine salt crystallised well from moist ethyl acetate, and systematic fractional crystallisation (the head fraction being crystallised five times) gave optically pure *l-cis*-3-methyl*cyclo*hexyl quinine phthalate (14·3 g.) of indefinite m. p., $[\alpha]_D$ −95·0° (chloroform; *c*, 2·0). The quinine salt was decomposed by running a solution in boiling alcohol into cold dilute hydrochloric acid and working up in the usual way. The resulting ester when recrystallised from light petroleum gave *l-cis*-3-methyl*cyclo*hexyl hydrogen phthalate as coarse aggregates of large white prisms, m. p. 70—72°, $[\alpha]_D$ −27·0° (benzene; *c*, 5·0) (Found: C, 69·3; H, 6·95. Calc.: C, 68·7; H, 6·9%). Hydrolysis of the hydrogen phthalate in the usual way gave a 95% recovery of *l-cis*-3-methyl*cyclo*hexanol, b. p. 84°/13 mm.; $n_D^{20°}$ 1·4582; $d_{4°}^{20°}$ 0·9135; $\alpha_D^{20°}$ − 6·7° (homogeneous). A series of derivatives of the active alcohol was prepared, a sample of the hydrogen phthalate being formed because Godchot and Canquil (*Compt. rend.*, 1934, **198**, 663) reported it as a liquid whereas Gough, Hunter, and Kenyon (*J.*, 1926, 2052) recorded m. p. 70—71°. In agreement with the latter workers the prepared sample when recrystallised from light petroleum had m. p. 70—72° identical with that of the specimen from the quinine salt. *l-cis*-3-Methyl*cyclo*hexyl *p*-nitrobenzoate, pale yellow glistening needles from methanol, had m. p. 81·5—82·5°, $[\alpha]_D$ − 27·2° (chloroform; *c*, 5·0) (Found: C, 64·1; H, 6·6. Calc.: C, 63·85; H, 6·5%). l-cis-3-*Methyl*cyclo*hexyl* 3 : 5-*din'trobenzoate* separated as pale yellow fluffy needles from aqueous alcohol, m. p. 134—135°, $[\alpha]_D$ − 15·2° (chloroform; *c*, 2·0) (Found: C, 54·5; H, 5·35; N, 8·9. $C_{14}H_{16}O_6N_2$ requires C, 54·5; H, 5·2; N, 9·1%). *l-cis*-3-Methyl*cyclo*hexylphenylurethane, needles from light petroleum, had m. p. 90—91·5°, $[\alpha]_D$ − 15·5° (chloroform; *c*, 5·0) (Found: C, 72·4; H, 8·15. Calc.: C, 72·05; H, 8·2%). l-cis-3-*Methyl*cyclo*hexyl*-α-*naphthylurethane*, needles from aqueous alcohol, had m. p. 117·5—118·5°, $[\alpha]_D$ − 19·4° (chloroform; *c*, 5·1) (Found: C, 76·55; H, 7·5. $C_{18}H_{21}O_2N$ requires C, 76·25; H, 7·45%).

d-cis-3-*Methyl*cyclo*hexanol.*—The mixture of hydrogen phthalates recovered from the mother liquors after the initial separation of the quinine salt (above) had $[\alpha]_D$ + 14° approx., indicating a content of about 75% of the *d*-ester. The crude hydrogen phthalate (13 g.) and strychnine (11·7 g.) were dissolved in chloroform–light petroleum (1 : 1 by volume; 130 c.c.). After removal of the first crop of crystals further quantities of ester (10 g.) and alkaloid (9 g.) were dissolved in the mother liquor, and after removal of the alkaloidal salt the process was repeated twice, using in all hydrogen phthalate (43 g.) and strychnine (38·5 g.; 0·7 mol.). The combined strychnine salt was systematically crystallised from chloroform–light petroleum (1 : 1; 8 vols.), the head fraction being recrystallised five times and the tail fraction nine times. Pure *d-cis*-3-methyl*cyclo*hexyl strychnine phthalate (41 g.) was obtained having m. p. 131—133°, $[\alpha]_D$ − 11·6° (chloroform; *c*, 5·0). The salt effervesced on melting and apparently retained some chloroform very tenaciously and concordant analysis could not be obtained. It was decomposed by adding a concentrated solution in alcohol to excess of cold, dilute hydrochloric acid. d-cis-3-*Methyl*cyclo*hexyl hydrogen phthalate*, isolated and purified in the usual way, had m. p. 70—72°, $[\alpha]_D$ + 27·2° (benzene; *c*, 5·0) (Found: C, 68·8; H, 7·1. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). Hydrolysis of the hydrogen phthalate gave *d-cis*-3-methyl*cyclo*hexanol, $\alpha_D^{21°}$ + 6·67° (homogeneous), $n_D^{20°}$ 1·4581, $d_{4°}^{20°}$ 0·9137. This yielded a *p*-nitrobenzoate, m. p. 80—81°, $[\alpha]_D$ + 27·8° (chloroform; *c*, 5·0).

dl-trans-3-*Methyl*cyclo*hexyl* 1-*Menthylaminoacetate.*—A sample of the *dl*-alcohol (10 g.) was dissolved in dry benzene and chloroacetyl chloride (10 g.) in the same solvent (30 c.c. in all) added, and the mixture was refluxed ($CaCl_2$ tube) until no more hydrogen chloride was evolved (1·5 hours). The cooled solution was washed successively with water, dilute sodium carbonate solution, and water, and dried ($MgSO_4$). After removal of the solvent on the water-bath, distillation under reduced pressure gave *dl-trans*-3-methyl*cyclo*hexyl chloroacetate (16·1 g.) as a colourless liquid, b. p. 99°/2 mm., $d_{4°}^{20°}$ 1·0765, with the fragrant odour characteristic of chloroacetates of *cyclo*hexane alcohols. The chloroacetate was dissolved in dry benzene (100 c.c.) and after the addition of *l*-menthylamine (32 g.; 2·5 mols.) the solvent was distilled off from a glycerol-bath and the temperature of the mixture raised to 150°. This temperature was maintained for 3·5 hours, and solid *l*-menthylamine hydrochloride slowly separated. The cooled mixture was poured into dilute sulphuric acid, chloroform added, and all well shaken to give an aqueous extract of menthylamine. After the chloroform layer had been washed successively with

water, 10% sodium carbonate solution, and water, and dried ($MgSO_4$), the solvent was removed (finally under reduced pressure) and left the menthylglycine derivative as a brownish oil (26 g.) which did not solidify. Accordingly the menthylglycine derivative was dissolved in chloroform and shaken with *N*-sulphuric acid, and the acid layer was separated and extracted with chloroform. The combined chloroform solutions were washed with water and dried, and the solvent was removed. The hard yellow solid residue (30 g.) was washed with a little light petroleum to remove colour, and after crystallisation from ethyl acetate (200 c.c.) the menthylglycine sulphate was obtained as a white crystalline solid, m.p. 141—143°, $[\alpha]_D$ — 45·6° (chloroform; *c*, 2·0). Systematic fractional crystallisation from ethyl acetate (five times) gave l-trans-3-*methyl*cyclo*hexyl* l-*menthylaminoacetate sulphate* (1·6 g.), fine white needles, m. p. 171—172·5°, $[\alpha]_D$ — 57·3° (chloroform; *c*, 2·0) identical with an authentic sample prepared from a sample of *l*-trans-3-methyl*cyclo*hexanol derived from pulegone [Found: C, 63·75; H, 10·1; N, 3·95; S, 4·3. $(C_{19}H_{35}O_3N)_2,H_2SO_4$ requires C, 63·6; H, 10·1; N, 3·9; S, 4·45%]. Subsequent preparations gave similar results, but as less than 10% of the optically pure sulphate was obtained from the crystallisations, and as little satisfactory material was isolated from the less pure fractions the method was abandoned. The picrate prepared from the *dl*-menthylglycine separated as yellow prisms from light petroleum and had m. p. 112—113°, $[\alpha]_D$ — 9·0°. Repeated crystallisation failed to alter the rotation. As a sample of the picrate prepared from the *l*-menthylglycine had the same crystalline form and m. p., with $[\alpha]_D$ — 20·5°, it was evident that this salt was of no value as a resolving agent. The *d*-tartrate, hydrochloride, and phosphate, and the *p*-nitrobenzoyl derivative were prepared from the menthylglycine, but none of them could be induced to crystallise.

Resolution by the Strychnine Salt.—Of the common alkaloids, brucine, cinchonidine, and strychnine gave crystalline salts with the *dl-trans*-hydrogen phthalate, and of these the strychnine *salt* appeared to have the sharpest m. p. and the best crystallising power. The salt has a low solubility in all organic solvents apart from chloroform and dioxan, even at the boiling point. In ethyl acetate it has a solubility of about 1 in 60 at the boiling point and 1 in 1000 at laboratory temperature. Recrystallised from this solvent it separated as large transparent rods with pyramidal ends, and showed marked birefringence. It had m. p. 168—170° $[\alpha]_D$ — 29·0° (chloroform; *c*, 2·0) (Found: C, 71·7; H, 6·9. $C_{36}H_{40}O_6N_2$ requires C, 72·4; H, 6·7%). In the preparation of the strychnine salt for resolution it was found best to add only 65—70% of the required amount of the alkaloid to a 2% solution of the hydrogen phthalate in boiling ethyl acetate. To the phthalate (25 g.) in boiling ethyl acetate (1·5 l.) finely powdered strychnine (23 g.) was added and boiling continued for 1 hour. Traces of undissolved solid were separated, and the filtrate was left overnight at room temperature after seeding with pure *l-trans*-strychnine salt. The alkaloidal salt (25·5 g.) was separated and the filtrate used again for a second preparation. The combined yield of strychnine salt (63 g.) represented 64% of the *dl*-hydrogen phthalate used. It was fractionally crystallised from ethyl acetate, each fraction being left at room temperature for at least 8 hours before being filtered. The head fraction was recrystallised seven times and the tail fraction twelve times before optical purity was reached. It was found necessary to follow the course of the resolution by occasional hydrolysis of the salt and isolation of the methyl*cyclo*hexanol, as after a certain stage very slight changes in the physical constants of the strychnine salt are accompanied by considerable alteration in optical purity. The strychnine salt had m. p. 168—171°, $[\alpha]_D$ — 30·0° (chloroform; *c*, 2·0), and represented a recovery of about 30% of the original hydrogen phthalate.

Decomposition of the Strychnine Salt.—The strychnine salt was easily soluble in boiling dioxan, and this simplified its decomposition. The salt (50 g.) in boiling dioxan (150 c.c.) was stirred into cold dilute hydrochloric acid (1 l. of 1%). The free hydrogen phthalate separated as an oil, but with this dilution of acid no separation of strychnine hydrochloride took place. The phthalate was quickly extracted with ether (thrice) and the combined extracts were washed with water and dried ($CaCl_2$). Solvent was removed on the water-bath, and traces of dioxan under reduced pressure. The residue, when boiled with a little light petroleum and cooled, gave transparent, acicular crystals of *l-trans*-3-methyl*cyclo*hexyl hydrogen phthalate having m. p. 94°, $[\alpha]_D$ — 13·0° (Found: C, 68·75; H, 7·0. Calc.: C, 68·65; H, 6·9%). Hydrolysed in the usual way, the ester gave 95% yield of *l-trans*-3-methyl*cyclo*hexanol, b. p. 94°/12 mm., $\alpha_D^{28°}$ — 3·62° (homogeneous), $n_D^{20°}$ 1·4573, $d_4^{20°}$ 0·9070.

Resolutions of the *dl*-hydrogen phthalate were also carried out with brucine and cinchonidine, but strychnine was more suitable. *l-trans*-3-Methyl*cyclo*hexyl brucine phthalate separated as sheaves of fine white needles having m. p. 179—180°, $[\alpha]_D$ — 31·0° (chloroform; *c*, 2·0). *l-trans*-3-Methyl*cyclo*hexyl cinchonidine phthalate formed large white needles which melted indefinitely at 102—108°, and had $[\alpha]_D$ — 62·5°.

Derivatives of *l-trans*-3-methyl*cyclo*hexanol were prepared by standard methods. The *p*-nitrobenzoate, pale yellow, shining scales from methanol, had m. p. 46—47° (Found: C, 64·15; H, 6·65. Calc.: C, 63·85; H, 6·5%). The 3:5-*dinitrobenzoate*, yellow needles from aqueous alcohol, had m. p. 97—98° (Found: C, 54·4; H, 5·35. $C_{14}H_{16}O_6N_2$ requires C, 54·5; H, 5·2%). The phenylurethane, stout shining needles from aqueous alcohol, had m. p. 117—118°, $[\alpha]_D$ — 20·0° (chloroform; *c*, 5·0) (Found: C, 71·9; H, 8·2. Calc.: C, 72·05; H, 8·2%). The *α-naphthylurethane*, woolly mass of needles from light petroleum, had m. p. 147—148° (Found: C, 76·4; H, 7·4. $C_{18}H_{21}O_2N$ requires C, 76·25; H, 7·45%).

d-trans-3-*Methyl*cyclo*hexanol.*—The mother liquors from the initial separation of the crude *l*-strychnine salt when decomposed yielded a hydrogen phthalate having $[\alpha]_D$ + 8° approx. As no alkaloidal salt could be prepared which allowed the *d-trans*-salt to be freed by crystallisation from a more soluble *l*-salt, attempts were made to effect a resolution by precipitation of the *l*-strychnine salt from solutions of the crude *d*-alkaloidal salt. This was in fact achieved by dissolving the dextrorotatory phthalate in chloroform and adding as much strychnine as would dissolve in the boiling solution. Light petroleum was added to incipient precipitation, and slow cooling then gave a deposit consisting of some free strychnine, heavy grains of the *l-trans*-strychnine salt, and many fine white needles. These were separated as far as possible mechanically, and recrystallised from hot chloroform by the addition of light petroleum. Free strychnine separated at each stage, indicating that the *d-trans*-salt was dissociating in solution. By continuing this method crude *d-trans*-hydrogen phthalate (60 g.) gave fine

needles (7·7 g.). The salt was decomposed to the hydrogen phthalate and the ester hydrolysed to *d-trans*-3-methyl*cyclo*hexanol, which had α_D + 3·31° (homogeneous), indicating a content of about 96% of the *d*-alcohol. In view of the poor yield of the product and the optical impurity, the method was not regarded as satisfactory.

Separation of d-trans-3-*Methyl*cyclo*hexanol as Phenylurethane*.—Experiments with mixtures showed that it was possible to separate the phenylurethane of the *l-trans*-alcohol from the *dl*-form by crystallisation from dilute alcohol, in which the *l-trans*-derivative is much less soluble. Accordingly part of the impure *d-trans*-hydrogen phthalate (above) was hydrolysed and the derived alcohol converted to the phenylurethane (10·5 g.); when systematically crystallised from aqueous alcohol (70%), this ultimately yielded pure d-trans-3-*methyl*cyclo*hexylphenylurethane* (6 g.), m. p. 117—118°, $[\alpha]_D$ + 19·8° (chloroform; *c*, 5·0) (Found: C, 72·15; H, 8·3. $C_{14}H_{19}O_2N$ requires C, 72·05; H, 8·2%).

Oxidation of Optically Pure 3-*Methyl*cyclo*hexanols*.—*l-cis*-3-Methyl*cyclo*hexanol (3 g.) in water (20 c.c.) containing potassium dichromate (3 g.) was oxidised by gradual addition of dilute sulphuric acid (3 c.c. of concentrated acid in 10 c.c. of water) so that the temperature rose to and was maintained at 50—60°. Worked up in the usual way, *d*-3-methyl*cyclo*hexanone (2·3 g.) was obtained having b. p. 63°/10 mm., $\alpha_D^{21°}$ + 11·5° (homogeneous), $n_D^{20°}$ 1·4454, $d_4^{20°}$ 0·9089. Oxidation of the *l-trans*-alcohol gave a sample of ketone having $\alpha_D^{23°}$ + 11·7°. The *l*-menthylhydrazone had m. p. 131—133°, $[\alpha]_D$ − 65·3° (chloroform; *c*, 2·1), − 60·9° (ethanol; *c*, 5·0).

Oxidation of *d-cis*-3-methyl*cyclo*hexanol in a similar way gave a good yield of *l*-3-methyl*cyclo*hexanone having $\alpha_D^{21°}$ − 11·5° (homogeneous), $n_D^{20°}$ 1·4452, $d_4^{20°}$ 0·9088. The *l*-menthylhydrazone had m. p. 146°, $[\alpha]_D$ − 18·5° (chloroform; *c*, 2·0), − 31·7° (ethanol; *c*, 4·8).

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JOHNSON CHEMICAL LABORATORIES, UNIVERSITY OF ADELAIDE. [*Received, June 3rd*, 1946.]

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50. *The Structure of Molecular Compounds. Part III. Crystal Structure of Addition Complexes of Quinol with Certain Volatile Compounds.*

By D. E. PALIN and H. M. POWELL.

A detailed determination, mainly by three-dimensional Fourier methods, has shown that in the compounds considered quinol molecules link together through hydrogen bonds to form infinite three-dimensional complexes of trigonal symmetry. The resulting giant molecule has a form, imposed by the dimensions of the quinol molecule and the disposition of the hydrogen bonds, so open that two such giant molecules are built up completely interpenetrating each other but having no direct attachment. In cavities enclosed simultaneously by the two giant molecules are located the molecules of the second volatile component which cannot escape from its surroundings. The composition $3C_6H_4(OH)_2,M$ is determined by the number of spaces available for the second molecule M. For the case where M is sulphur dioxide the co-ordinates of all atoms of the quinol framework have been found. The position of the sulphur dioxide and its rotation about one axis have also been established by Fourier analysis. In the quinol molecules the interatomic distances found (to within about ± 0·03 A.) are C–C 1·39, C–O 1·36, OH . . . O 2·75 A. The hydroxyl groups are arranged in hydrogen-bonded hexagons. The analysis involves some special applications of Patterson methods which here are able to establish the presence of a symmetry centre and to locate most of the atoms in a direct manner.

IN addition to the usual type of molecular compound formed by phenols with other substances such as aldehydes, quinol forms a series of complexes with certain volatile compounds of the general type 3(or 4)$C_6H_4(OH)_2$,M, where M denotes the second molecule, *viz.*, H_2S (Wohler, *Annalen*, 1849, **69**, 297), SO_2 (Clemm, *ibid.*, 1859, **110**, 357), $H{\cdot}CO_2H$ and HCN (Mylius, *Ber.*, 1886, **19**, 999), HCl (Schmidlin and Lang, *ibid.*, 1910, **43**, 2817), HBr (Gomberg and Cone, *Annalen*, 1910, **376**, 238), $CH_3{\cdot}OH$ (Palin and Powell, *Nature*, 1945, **156**, 334), $CH_3{\cdot}CN$ (*idem*, unpublished). These compounds are very stable under ordinary conditions of storage, and have no smell of the volatile substance, but are decomposed into their components when heated to near their melting points or dissolved in water. Mylius (*loc. cit.*) from a series of experiments with the formic acid complex concluded that no ordinary chemical combination exists. He suggested that during crystallisation the quinol molecules were somehow able to lock the volatile component in position. It was thought that the crystal structure of this class of compound would be of interest in that it would show the way in which the second component is retained and at the same time give some information on the structure of quinol itself. This communication is mainly concerned with a detailed determination of the structure of the complex with sulphur dioxide.

Crystals of the compound were prepared by slow crystallisation from a solution of quinol

in water which was saturated with sulphur dioxide. Chemical analysis gives a somewhat lower sulphur dioxide to quinol ratio than the 1 : 3 value given by Clemm (*loc. cit.*), suggesting that this is not a stoicheiometric compound. The point is discussed further below. The compound, stable at room temperature, has no smell of sulphur dioxide which is, however, set free quantitatively when the substance is dissolved in water, alcohol, or ether, or heated to the melting point. A trace of sulphur dioxide, detectable by smell, is given off from the material ground in a mortar.

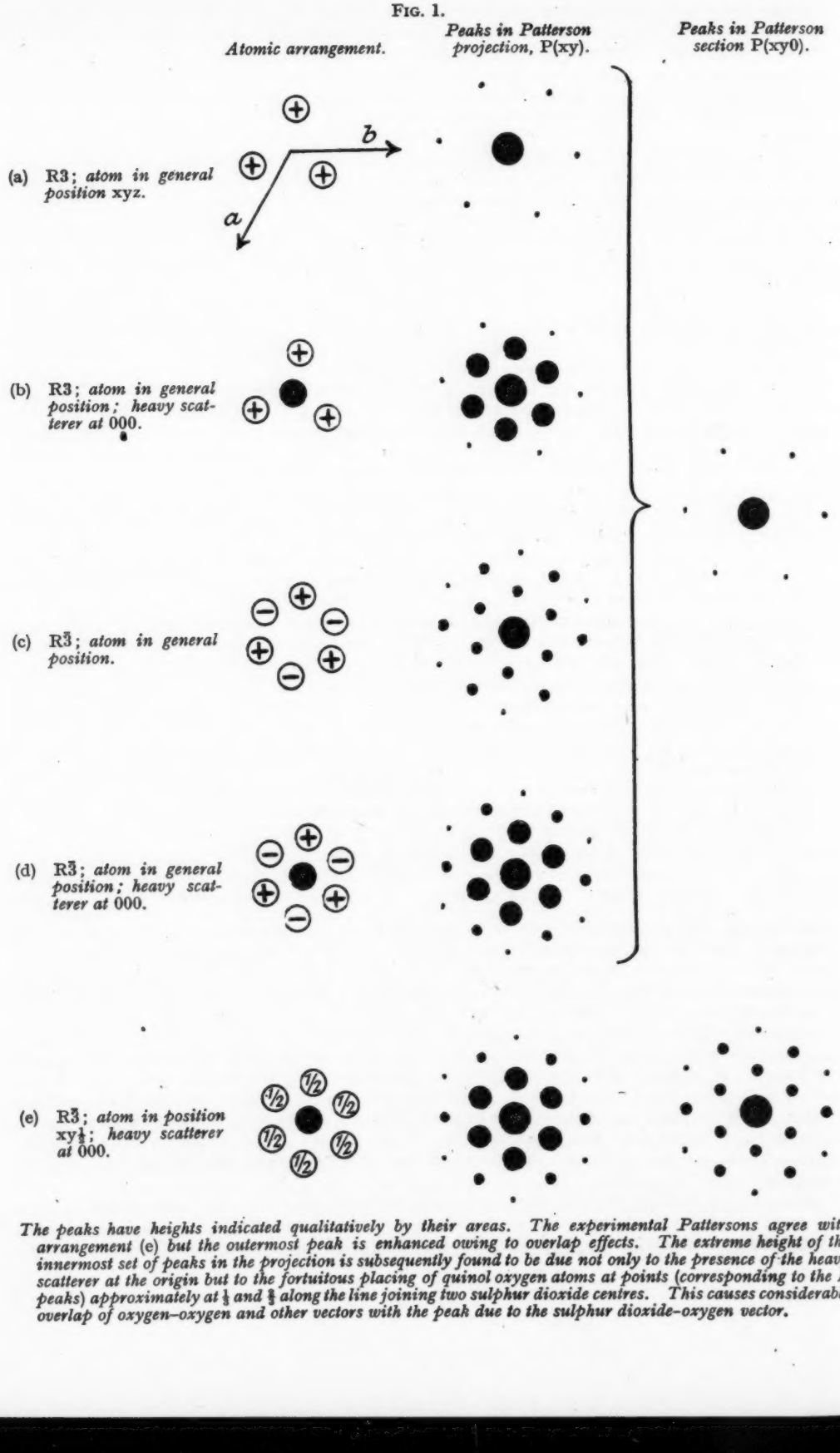
The yellow crystals form six-sided prisms of the form $\{11\bar{2}0\}$ terminated by rhombohedral faces $\{10\bar{1}1\}$. They are optically uniaxial with weak positive birefringence and are harder than most organic crystals. The unit cell dimensions found were $a = 16{\cdot}29 \pm 0{\cdot}03$, c $5{\cdot}81 \pm 0{\cdot}02$ kX referred to hexagonal axes, or $a = 9{\cdot}6$ kX, $\alpha = 116\frac{1}{2}°$ referred to rhombohedral axes. The density $1{\cdot}440 \pm 0{\cdot}005$ g./c.c., determined by flotation, gives a molecular weight of 1165. This corresponds approximately to three molecules of $SO_2,3C_6H_4(OH)_2$ per hexagonal unit cell (equivalent to one molecule per rhombohedral cell).

Oscillation photographs taken about axes perpendicular to (0001), $(11\bar{2}0)$ and $(10\bar{1}0)$ showed a characteristic appearance due to absence of spectra $h - k + l \neq 3n$ which established the rhombohedral lattice, and lack of vertical planes of symmetry, as shown by a [0001] zero layer line Weissenberg photograph, reduced the space-group possibilities to $R\bar{3}$ or $R3$ which differ in that $R\bar{3}$ has a centre of symmetry and $R3$ has not. Although there are similar rhombohedral faces at each end, the centrosymmetric nature of the crystals was at first open to doubt since " β-quinol " (Caspari, *J.*, 1927, 1093) which also has $(11\bar{2}0)$ prisms, very similar cell dimensions and (as reported) nine molecules of quinol per unit cell, has, in contrast, dissimilar terminal faces which point to the absence of a symmetry centre. But tests for piezoelectricity by a modification of the Giebe and Scheibe circuit (*Z. Physik*, 1925, **33**, 760) and for pyroelectricity by the liquid-air method (Martin, *Min. Mag.*, 1931, **22**, 519) gave negative results with the sulphur dioxide compound and it was considered reasonable to assume the space-group $R\bar{3}$ for purposes of an attempted direct solution. The stages of the subsequent analysis are not, however, based on the assumption of centrosymmetry but are used to confirm it. Since the only electron-density projection expected to give useful information was that seen along the c axis, it was decided to use three-dimensional methods where necessary. Equi-inclination Weissenberg photographs were therefore taken about the [0001] axis of small crystals of approximately cylindrical shape. The required intensity range was covered by means of two exposures and multifilm technique (de Lange, Robertson, and Woodward, *Proc. Roy. Soc.*, 1939, *A*, **171**, 404). Copper-K_α radiation was used. Intensities, estimated visually and correlated for different layer lines by factors obtained from photographs about other axes, were divided by their corresponding Lorentz polarisation-rotation factors to give a set of F^2 and hence F_{hkil} values. In this way relative F^2 and F values were obtained for nearly 200 *hkil*, with orders of h and k up to 19 and l up to 3, and $10^{-8} \sin\theta/\lambda > 0{\cdot}6$. Each of these was included the required number of times with different but related indices in any Fourier summation.

The space-group requirements of $R\bar{3}$ as they affect this compound are as follows. Since there are nine molecules of quinol per unit cell, their centres must lie in special positions $\frac{1}{2}0\frac{1}{2}$, $0\frac{1}{2}\frac{1}{2}$, $\frac{1}{2}\frac{1}{2}\frac{1}{2}$, with the equivalents at $+ (\frac{1}{3}\frac{2}{3}\frac{1}{3})$ and $+ (\frac{2}{3}\frac{1}{3}\frac{2}{3})$, and the asymmetric unit consists of one half of the centrosymmetric quinol molecule. The non-centrosymmetric sulphur dioxide molecule with $\widehat{OSO}$ angle $\approx 120°$ cannot as a whole fit into the space-group unless it is rotating or molecules take up various orientations in different cells to give statistically the $R\bar{3}$ symmetry. The sulphur atom alone could be placed in the threefold position at the origin or the oxygen atoms in a sixfold position at $\pm 00z$, but these conditions together would require a linear sulphur dioxide molecule. For a rotating molecule the space-group symmetry may be satisfied in several ways. With sulphur at the origin the oxygens must revolve round the c axis to give the trigonal symmetry, and if they remain in planes at $\pm z$ an effective symmetry centre is also introduced. If, instead, the oxygen atoms are placed at $\pm 00z$ the sulphur atom then moves over a circle round the c axis at $z = 0$. If neither sulphur nor oxygen occupies fixed positions rotation about an axis, *e.g.*, through the centre of gravity of the molecule such that all atoms describe circles round the c axis, sulphur at $z = 0$ and oxygen at $\pm z$, produces the same symmetry. These are the minimum requirements but other rotations and oscillations may be superposed.

Since it thus appears that the sulphur dioxide molecule would lie, as a whole, close to the c axis an attempt was made to obtain an approximate electron-density projection perpendicular to this axis by assuming the space-group $R\bar{3}$ and giving all the F_{hki_0} values the positive sign.

FIG. 1.

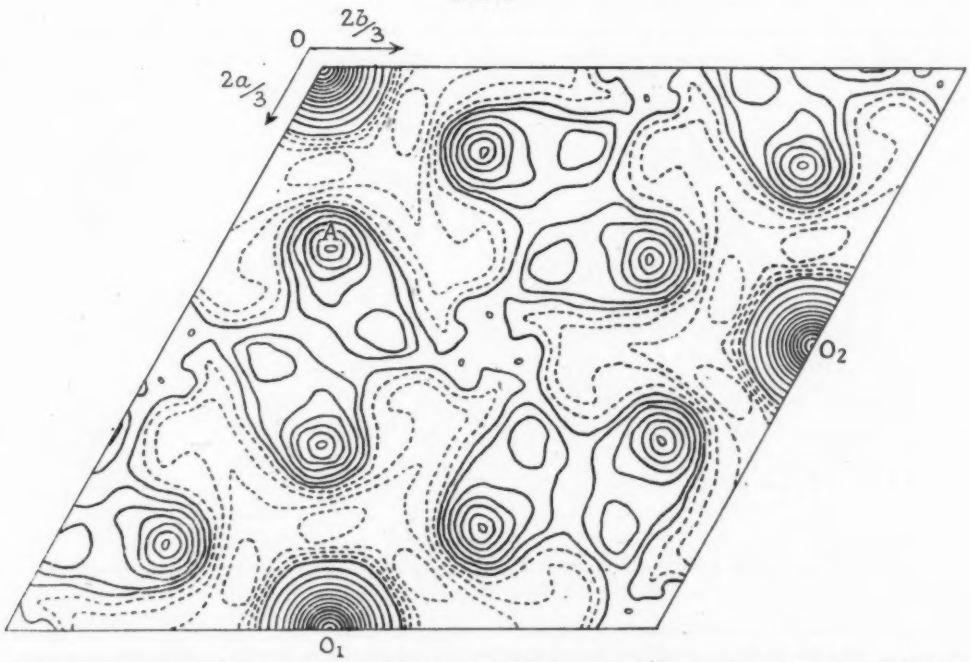

Atomic arrangement.
Peaks in Patterson projection, P(xy).
Peaks in Patterson section P(xy0).
(a) R3; atom in general position xyz.
b
a
(b) R3; atom in general position; heavy scatterer at 000.
(c) R$\bar{3}$; atom in general position.
(d) R$\bar{3}$; atom in general position; heavy scatterer at 000.
(e) R$\bar{3}$; atom in position xy$\frac{1}{2}$; heavy scatterer at 000.
1/2

The peaks have heights indicated qualitatively by their areas. The experimental Pattersons agree with arrangement (e) *but the outermost peak is enhanced owing to overlap effects. The extreme height of the innermost set of peaks in the projection is subsequently found to be due not only to the presence of the heavy scatterer at the origin but to the fortuitous placing of quinol oxygen atoms at points (corresponding to the* A *peaks) approximately at* $\frac{1}{3}$ *and* $\frac{2}{3}$ *along the line joining two sulphur dioxide centres. This causes considerable overlap of oxygen–oxygen and other vectors with the peak due to the sulphur dioxide–oxygen vector.*

The structure factor contributions of the sulphur dioxide will be positive for all except high indices, and it was possible that they might have been large enough to outweigh the effects of the lighter atoms for so many reflexions that the positions of other atoms would be indicated in the first approximate electron-density projection so obtained. From the resulting projection it appears that the structure could have been found in this way, but in view of doubts concerning the space-group it was decided to develop it afresh by application of Patterson (*Z. Krist.*, 1935, **90**, 517) and Harker (*J. Chem. Physics*, 1936, **4**, 381) F^2 Fourier synthesis, without the initial assumption of centrosymmetry.

Although the total number of peaks in the Patterson synthesis of a quite simple structure is very large, and interpretation is commonly difficult, there is sometimes a small region close to the origin where the peaks due to a single atom, symmetrically repeated in some way around the origin, may be observed comparatively free from distortion by other peaks. This may be expected when these atoms are linked at a short distance, and when for structural reasons it is impossible for any other set of linked atoms to be separated at the same or nearly the same

FIG. 2.



Patterson–Fourier projection P(xy) *on* (0001). *The interval between full contour lines near the origin is twice that used elsewhere.*

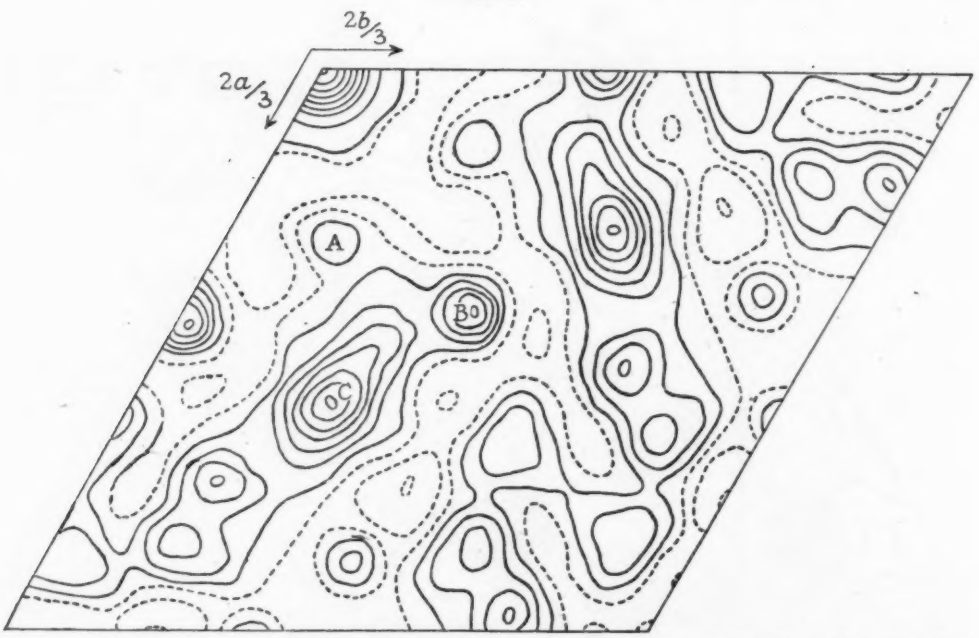
distances in similar directions. In Fig. 1 are shown the sets of Patterson peaks to be expected in a projection perpendicular to the *c* axis, and in a parallel section of the three-dimensional Patterson synthesis at $z = 0$. A single atom with its space-group equivalents is considered, and peak patterns for $R3$ and $R\bar{3}$ with and without the effect of a large scattering mass near to the *c* axis are indicated.

The Patterson projection as computed from observed F^2_{hk0} is reproduced in Fig. 2. It shows very high peaks *A* lying at one-third intervals nearly on lines joining the two origin peaks *O* and O_1. There is a fairly high plateau between the two *A* peaks and comparatively little elsewhere. There are combined together in this projection the effects of several light atoms and the heavy scattering sulphur dioxide which will give a number of superposed patterns similar to those in Fig. 1, together with other peaks due to interatomic vectors between atoms unrelated by symmetry. The great height of peaks *A* shows clearly that the structure must contain the heavy scatterer on the threefold symmetry axis as in (*b*), (*d*), or (*e*). The plateau suggests that the quinol molecules are placed somehow along lines joining the several pairs of origins, and the small peaks near the centre of Fig. 2 at *B* such that *OB* makes an angle of 30° to *OA* and *OB* =

$\sqrt{3}OA$ correspond to peaks that arise in (*b*), (*c*), (*d*), or (*e*) if there is an atom in a position corresponding to *A*.

In a Patterson section with $z = 0$, interatomic vectors between groups of three atoms related by the symmetry axis should produce sets of peaks similar in pattern to those shown in (*a*), and the overwhelming influence of the sulphur dioxide should be removed, since it can produce peaks in this section only in co-operation with any atoms which are accidentally at the same *z* level. In the computed section, Fig. 3, there are peaks *A* of an inner hexagon as required for (*a*), (*b*), (*c*) or (*d*), but there are also peaks *B* and *C* in positions similar to the additional peaks in the projections (but not the sections) for (*c*) and (*d*). The peak *c* may in part be due to vectors between sulphur dioxide and some part of the quinol molecule which, as previously found, must lie in this general direction, but *B* cannot be so explained and must therefore be due to lighter atoms only. Since it lies in the required direction at $\sqrt{3}$ times the distance of *A* from the origin, the simplest interpretation is that there is a planar group of six atoms in a regular hexagon in positions corresponding to the *A* peaks around the *c* axis. This will arise if the space-group is

FIG. 3.



Patterson–Fourier section P(xy0). *The interval between full contour lines near the origin is four times that used elsewhere.*

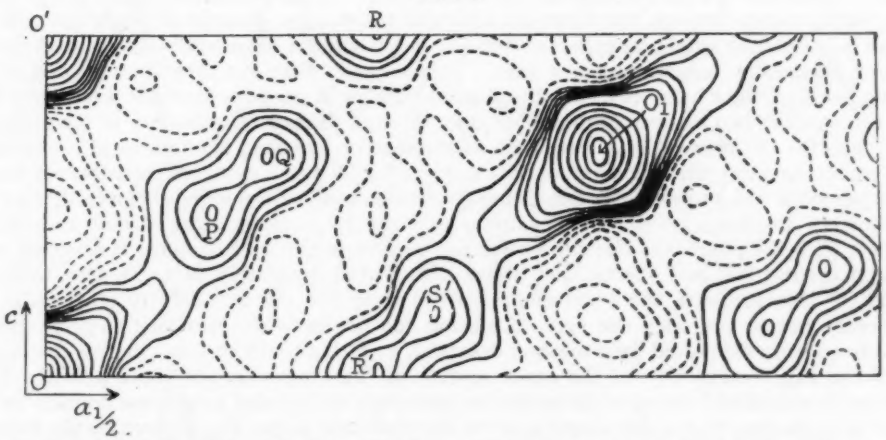
$R\bar{3}$ and the *z* co-ordinate of the atoms concerned is 0 or $\frac{1}{2}$. This inner hexagon has a side of approximately 2·8 A., such as would be expected for a set of six OH groups hydrogen-bonded in this form. Peak *A* may not give the exact position of the oxygen atoms since it may be distorted by nearby peaks due to other atoms.

If the sulphur dioxide molecule is rotating so that its centre is in the threefold position 000, the hexagon of oxygen atoms must be at $z = \frac{1}{2}$ because the relatively low height of the peak *A* in the Patterson section shows that the sulphur dioxide and the six oxygen atoms are not at the same *z* level. The greater height of peak *B* must be due to accidental overlapping with a peak due to some other pair of atoms, and the magnitude of the complex peak *C* suggests that it arises from vectors between sulphur dioxide and parts of the quinol molecules having the same *z* co-ordinates. The structure therefore appears to consist of quinol molecules arranged so that each oxygen atom lies on one corner of a hexagon round a trigonal axis, with the benzene ring connecting pairs of oxygen atoms which lie near different axes. Part of each quinol molecule will lie in or near a plane parallel to the *c* axis and passing through the origins *O* and O_1 (Fig. 2), and there should be important vectors between these parts and the sulphur dioxide molecule which is also contained in this plane. The Patterson–Harker section prepared after

transformation of the indices to orthohexagonal axes is for convenience plotted with reference to axes X_1YZ, where X_1 makes an angle of 30° with the original X axis. The section (Fig. 4) shows peaks $PQRS$ on a line joining the origin O to the origin O_1' at $z = 1\frac{1}{2}$, $PQ = RS \simeq 1{\cdot}4$, $QR \approx 2{\cdot}8$ A. Consideration of the probable size and shape of the quinol molecule leads to the conclusion that P gives the vector from the sulphur dioxide at the origin and the quinol oxygen atom, and Q gives the similar vector to the carbon atom to which this oxygen is attached. The simplicity of the pattern without other peaks shows that the quinol molecule is symmetrically placed between O and O_1' and thus again introduces a symmetry centre. The other four carbon atoms of the quinol molecule are necessarily out of the plane of this section.

The detailed structure could now be determined, and the final values of the parameters which give the positions of all atoms in the unit cell were reached in four successive stages described in more detail below. The Patterson analysis fixes the approximate position of the O–O axis of the quinol molecule, and the first set of co-ordinates was derived by selection of values in agreement with this and the further conditions that the quinol molecules must be hydrogen-bonded in such a way as to accommodate the sulphur dioxide molecule near to the origin, the O–C distance by analogy with that in resorcinol (Robertson, *Proc. Roy. Soc.*, 1936, *A*, **157**, 79; 1938, **167**, 122) should be about 1·36, the benzene ring a flat hexagon of side approximately 1·39, and the separations of non-bonded atoms not much less than 3·5 A. Within limits

FIG. 4.



Patterson–Fourier section $P(x_1 0z)$. *The interval between the innermost seven contours near the origin is four times that elsewhere.*

imposed by these conditions co-ordinates were selected by comparison of calculated structure factors with the observed values. These calculated values depend on the inclusion of a contribution for the sulphur dioxide molecule. The preliminary estimates of this quantity were sufficiently accurate to give a substantial number of correct signs for the structure factors, and the subsequent stages all consisted of electron-density Fourier syntheses in which signs were revised or previously uncertain terms were included as the revised co-ordinates of the preceding stage permitted.

(1) Structure factors F_{hki0} were calculated for structures in which the O–O axis of the quinol molecules was fixed as described above, the sulphur dioxide contribution was calculated for a sulphur atom at the origin with two oxygen atoms imagined uniformly distributed over the surface of a sphere of radius 1·45 A. equal to the S=O bond distance, and the co-ordinates of the carbon atoms which are not fixed by the above considerations were given alternative values corresponding to various angles of twist, relative to the rest of the structure, of the plane of the benzene ring about the O–O axis. This was done for low-order reflexions from contoured structure factor graphs (Bragg and Lipson, *Z. Krist.*, 1936, **95**, 323). The atomic scattering factors used were calculated from the data given by Robertson (*Proc. Roy. Soc.*, 1935, *A*, **150**, 109) with an approximation for the hydrogen atoms. From the best agreement obtainable in this way a set of xy co-ordinates for all atoms was derived.

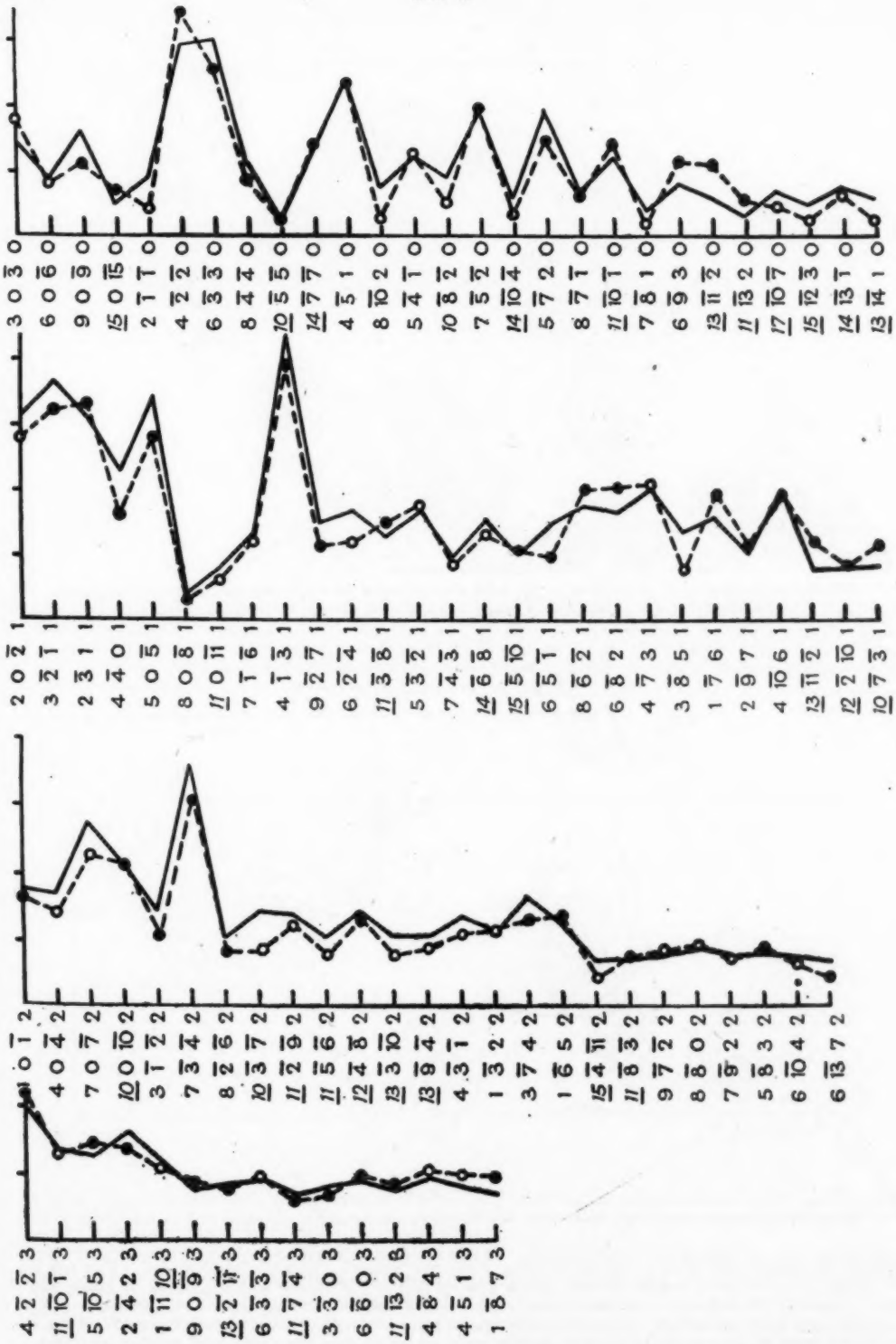
(2) The electron-density projection on (0001) was computed. The calculations of stage (1) provide the signs of F_{hki0} for lower orders but for higher orders, $10^{-8} \sin\theta/\lambda > 0{\cdot}42$, the compar-

atively large sulphur contribution was presumed to confer the positive sign in every case. From the projection obtained, which showed the sulphur dioxide as a single peak and the form of the quinol molecule without very clear resolution of the atoms, and from consideration of a model to show the general packing arrangements, z co-ordinates were estimated and revised values for xy obtained.

(3) The xyz values obtained in (2) were used to calculate F_{hkil}. The agreement was good for $l = 0$ and $l = 1$, and although it was not so good for $l = 2$ or 3 it was considered probable that the signs would be correct for all except the weak reflexions. All F values above a selected magnitude that seemed large enough to be incapable of sign reversal through any possible errors were therefore given the computed sign, and the remainder, consisting of about a quarter of those with $l = 1$, half of those with $l = 2$ and three-quarters of those with $l = 3$, were omitted from the first set of three-dimensional Fourier summations which were then carried out. By chance, the orientation of the quinol molecules and the rhombohedral symmetry combine to reveal the x and y co-ordinates of all four atoms of the quinol part of the asymmetric unit in suitable areas of the sections through the cell at $z = 0$ and $z = \frac{1}{2}$. The section ZX_1 passes nearly through the centres of carbon atoms C_1, C_1' and oxygen atoms O, O′ (see Fig. 11) of the quinol molecule, and a section parallel to this at $y = 0{\cdot}055$ passes nearly through the centres of the remaining carbon atoms C_2' and C_3. These four sections were computed and showed resolution of all atoms of the quinol part of the structure so that their combined results made it possible to estimate new xyz parameters for these atoms. An examination of the ZX_1 vertical section which passes through the supposed centre of the sulphur dioxide molecule showed that the peak is lower than would be expected if there were a sulphur atom at the origin, and there is a marked elongation parallel to the c axis. This suggests that the rotational motion of the molecule is about the c axis only, and the shape of the peak suggests that the axis of rotation passes through the two oxygen atoms rather than through the centre of gravity of the molecule.

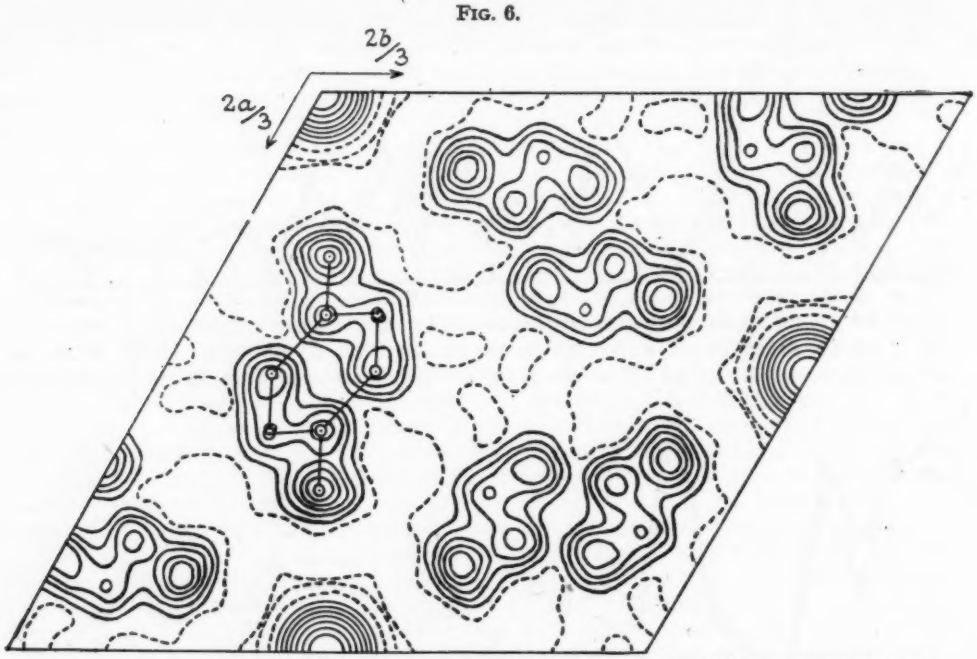
(4) Signs for all observed F_{hkil} were then determined on the basis of the revised co-ordinates for the carbon and oxygen of the quinol part as given by (3) and a modified contribution for the suilphur dioxide. The former approximation gives calculated values of F_{hkil}, especially for $l = 2$ or 3, showing discrepancies so long as sulphur and the two oxygen atoms are all regarded as associated with the point 000, but the agreement may be improved if sulphur is assumed to be in motion around 000 and the oxygen atoms are treated separately as units near to $\pm 00z$, $z = 0{\cdot}217$. This supports the conclusions derived from the electron-density sections in (3), but in order not to prejudge the type of motion too precisely the modified sulphur dioxide contributions were estimated by a method designed, as far as could be seen, to give the correct signs of the F_{hkil} irrespective of the exact motion of the atoms around these points. If an atom may be considered owing to its motion as uniformly distributed over some domain having a centre of symmetry at xyz, its contribution to the structure factor F_{hkl} is given by the expression $f'.e^{2\pi i(hx+ky+lz)}$ where f' is the atomic scattering factor f multiplied by a correction term which depends on the form of the uniformly occupied domain. This term is $(\sin z)/z$ for uniform distribution on the surface of a sphere, $z = 2\pi r/d_{hkl}$, r = radius of sphere, d_{hkl} = spacing of the plane for which the contribution is to be calculated. For uniform distribution on a circle of radius r the term is $J_0(z)$, $z = 2\pi r \sin\psi/d_{hkl}$, ψ is the angle between the normal to the circle and the normal to the plane hkl concerned, $J_0(z)$ is the Bessel coefficient of order zero of argument z. When $z = 0$, *e.g.*, for $r = 0$ or $\psi = 0$, the correction term is unity. For both cases mentioned the term changes, as z increases, according to somewhat similar curves; $(\sin z)/z$ first changes from positive to negative at $z = \pi$ and thereafter reverses sign at intervals of π, $J_0(z)$ first becomes negative at z slightly $> \frac{3}{4}\pi$ and thereafter reverses sign at points very close to $\frac{3}{4}\pi + n\pi$. The radius r cannot be large since the space available for these motions is restricted. In consequence r/d_{hkl} and therefore z is generally small and the correction term is a positive number less than unity. Owing to the form of the curves it is impossible to get large magnitudes of the correction term for the comparatively few instances among the high order reflexions where it might be negative. This is also true for any other type of small movement. Since there are also contributions to the structure factors from the fixed parts of the structure it is therefore very improbable that a wrong sign will be obtained if the sulphur and oxygen contributions are computed as though the atoms were at 000 and $\pm 00z$ and then diminished by a suitable factor without change of sign. A constant factor of $\frac{5}{8}$ was found to give a considerably improved agreement in the calculated F_{hkil} values for $l = 2$ or 3 and this itself confirms that the general direction of the modification is correct. The agreement of calculated and observed values for a number of reflexions may be seen from Fig. 5. With the signs thus determined, the projection and all the sections were repeated with inclusion of all the F_{hkil} values which had pre-

FIG. 5.



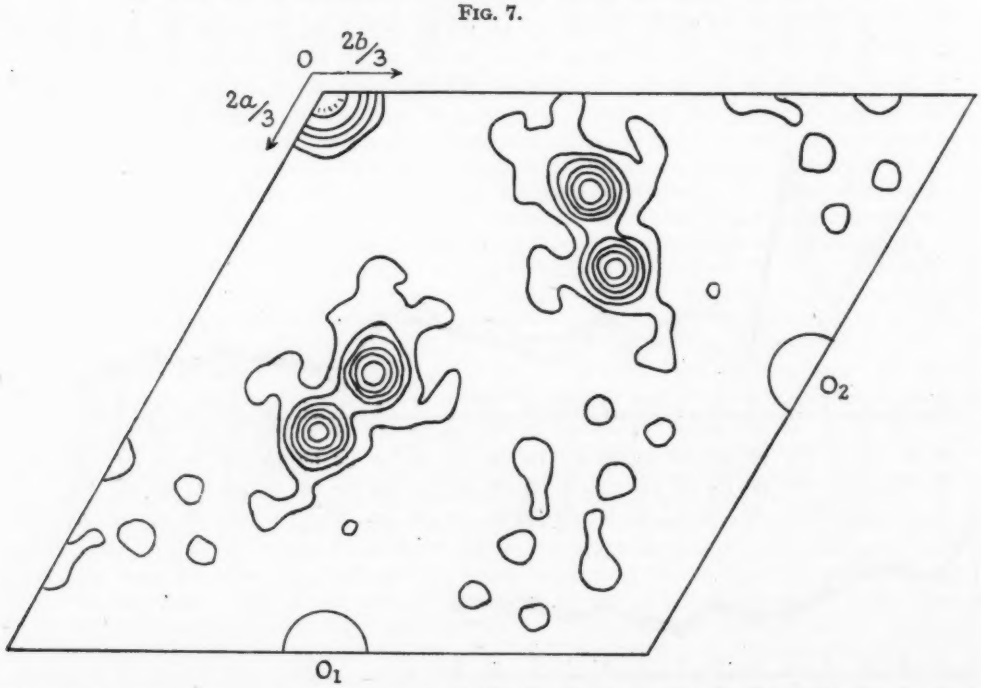
The calculated and the relative observed F_{hkl} *values for the principal reflexions reduced to approximately the same scale.* —— *Observed;* – – – *calculated* (● *positive,* ○ *negative*).

FIG. 6.



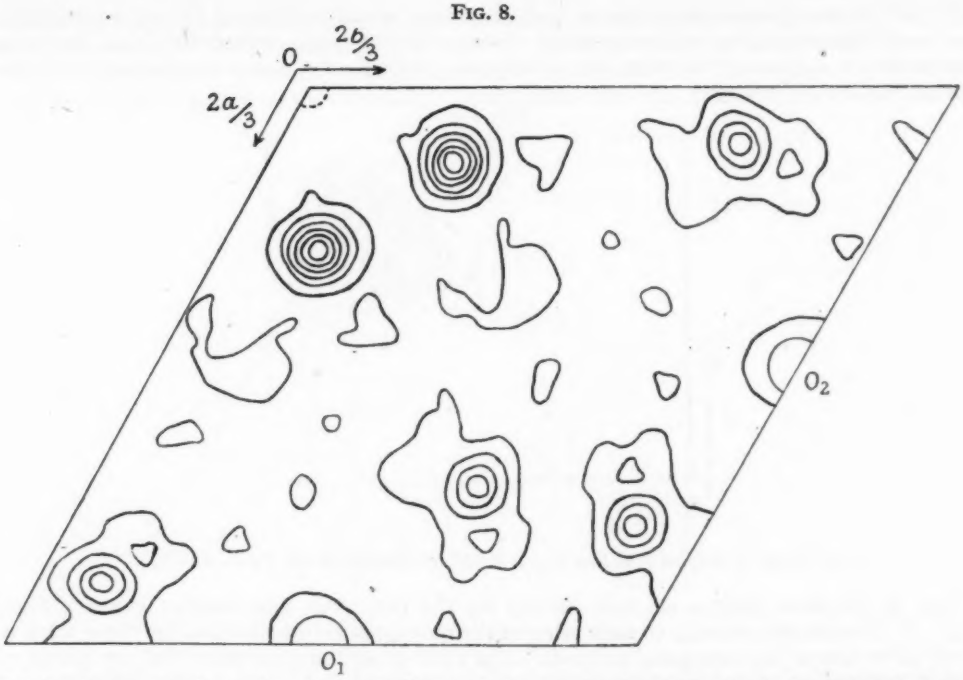
Relative electron-density projection ρ(xy), with atomic positions indicated for one quinol molecule. Sulphur dioxide appears as a single peak of circular symmetry at the origin.

FIG. 7.



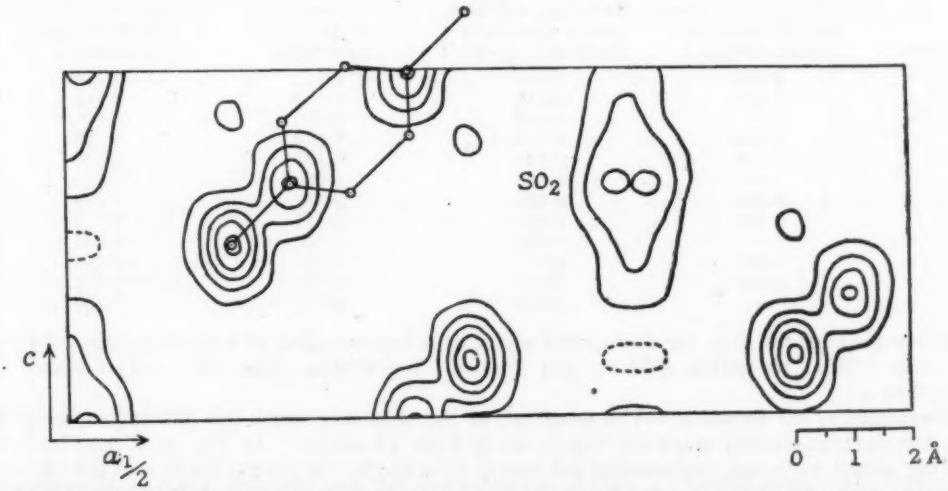
Relative electron-density section ρ(xy0), showing peaks for atoms C_1' and C_2' (see Fig. 11). The irregular areas of low electron density in this section and in that of Fig. 8 are mainly caused by atoms not in the plane of the section. The peak at the origin O has a small central depression, not shown by the contours, and arises from the rotation of the sulphur atom as described in the text. At O_1 and O_2 the section passes near to oxygen of the sulphur dioxide molecule on the side remote from the sulphur and shows a small peak (cf. Fig. 8).

FIG. 8.



Relative electron-density section $\rho(xy\frac{1}{2})$, *showing peaks for two oxygen atoms of a hydrogen-bonded hexagon and carbon atoms corresponding to* C_2 *and* C_3' (*see Fig.* 11). *At origin* O *the section, passing midway between two sulphur dioxide molecules, shows no peak, but at* O_1 *and* O_2 *it passes between the sulphur and one oxygen atom of a sulphur molecule and shows peaks. These accordingly have a higher electron density than the peaks in the corresponding positions in Fig.* 7.

FIG. 9.

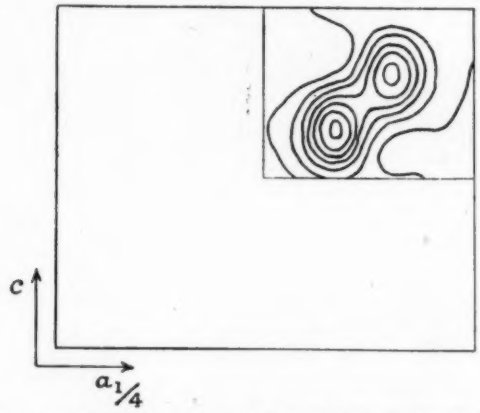


Relative electron-density section $(x_1 0z)$ *with peaks for* C_1C_1' *and for the oxygen atoms* O, O′ (*see Fig.* 11). *The projected positions of the other carbon atoms which are out of the section are also indicated.*

viously been omitted owing to uncertainty of signs. Marked improvements in the resolution and absence of spurious detail (most of the irregular areas of electron density which appear in addition to the principal peaks in Figs. 7 and 8 are due to atoms near the sections) further confirm the correctness of the sign determination. Co-ordinates of the carbon and oxygen atoms of the quinol part of the structure estimated from these new sections accord within narrow

limits with known interatomic distances, and, since they would be affected by any errors in the signs used, the remaining portions of the electron-density maps, calculated from the same experimental F values and the same computed signs, give direct evidence on the position of the sulphur dioxide (see below).

FIG. 10.



Relative electron-density section (x_1, $-0{\cdot}055$, z) *showing peaks for* C_2 *and* C_2'.

Figs. 6—10 show relative electron density for the projection and sections named; Figs. 11 and 12 show the relationship to each other of the nine quinol molecules and the three sulphur dioxide molecules of the hexagonal unit cell. The table gives the parameters for the atoms as found in the four successive approximations.

Atomic parameters as estimated in successive stages of the structure determination.

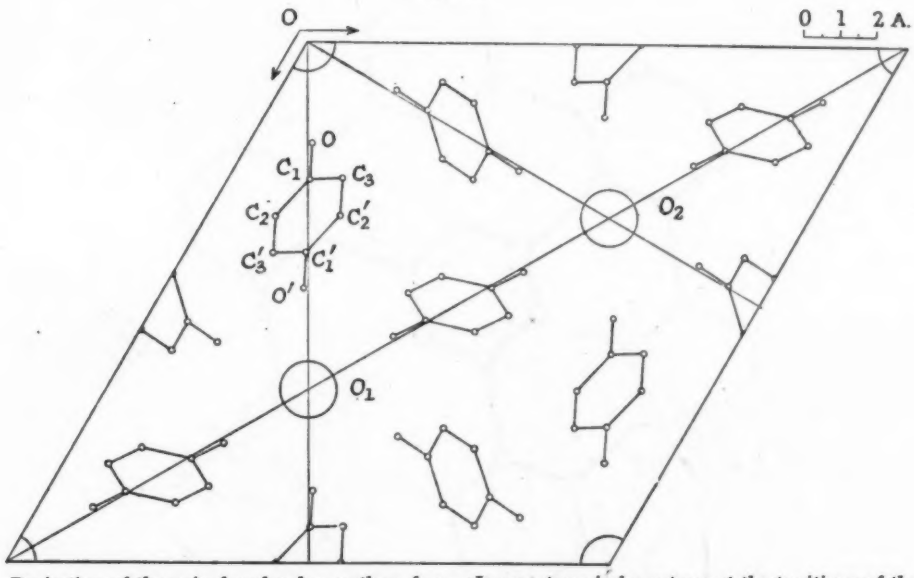
Atom.		(1) Patterson's and trial and error calculations of F_{Ah0}.	(2) First F_{Ah0} synthesis (some signs incorrect) and model.	(3) First F_{Ahl} syntheses to give sections. Many weak F's omitted (signs uncertain).	(4) Final syntheses with all F's. In calculation of signs, second modified form of SO_2 contribution included.
	x	0·193	0·198	0·192	0·195
O	y	0·106	0·104	0·103	0·105
	z	—	0·483	0·500	0·500
	x	0·264	0·266	0·262	0·263
C_1	y	0·138	0·135	0·133	0·135
	z	—	0·655	0·670	0·665
	x	0·345	0·329	0·340	0·334
C_2	y	0·127	0·108	0·117	0·113
	z	—	0·646	0·640	0·645
	x	0·260	0·270	0·262	0·262
C_3	y	0·181	0·198	0·188	0·188
	z	—	0·839	0·850	0·855

These parameters give for the quinol molecule a benzene ring of regular hexagonal form with side 1·39 A. to within 0·03 A., and C–O = 1·36±0·03 A. The OH . . . O distance is 2·75±0·03 A.

Discussion of the Structure.—The essentials of the structure which are difficult to visualise from the electron-density maps are illustrated in Figs. 13 and 14. In Fig. 13 it may be seen that the quinol molecules, represented for clarity by a single line joining the two oxygen atoms of one molecule, are linked through hydrogen bonds to form a giant molecule infinitely extended in three dimensions. Six oxygen atoms form a plane hexagon of side 2·75 A. parallel to the xy plane. The central lines of six quinol molecules extend alternately up and down from these oxygen atoms. The oxygen–oxygen axis of the molecule makes an angle of 45° with the plane of the oxygen hexagons, and, owing to an inclination of about 3° to the line joining the corresponding origins, makes two slightly different angles of average value 111°, *i.e.*, nearly the tetrahedral angle, with the hydrogen bonds at its ends. The angle between the plane of the benzene ring and the ZX_1 plane is 45°. Each of these six quinol molecules is connected in a

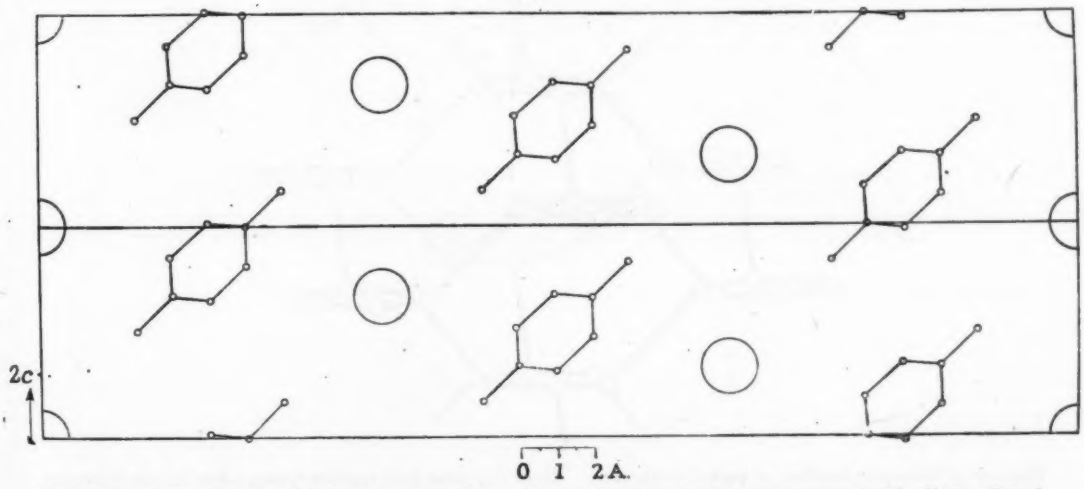
similar way through its other hydroxyl group to a separate oxygen hexagon parallel to but above or below the first. Continuation of this pattern of linkages produces an indefinitely extended set of linked cages of general rhombohedral shape as illustrated in the perspective drawing of Fig. 13. This is a very open structure. Comparison with the 2·75 A. sides of the hexagons

FIG. 11.



Projection of the quinol molecules on the c *face. Large open circles represent the positions of the sulphur dioxide molecules.*

FIG. 12.

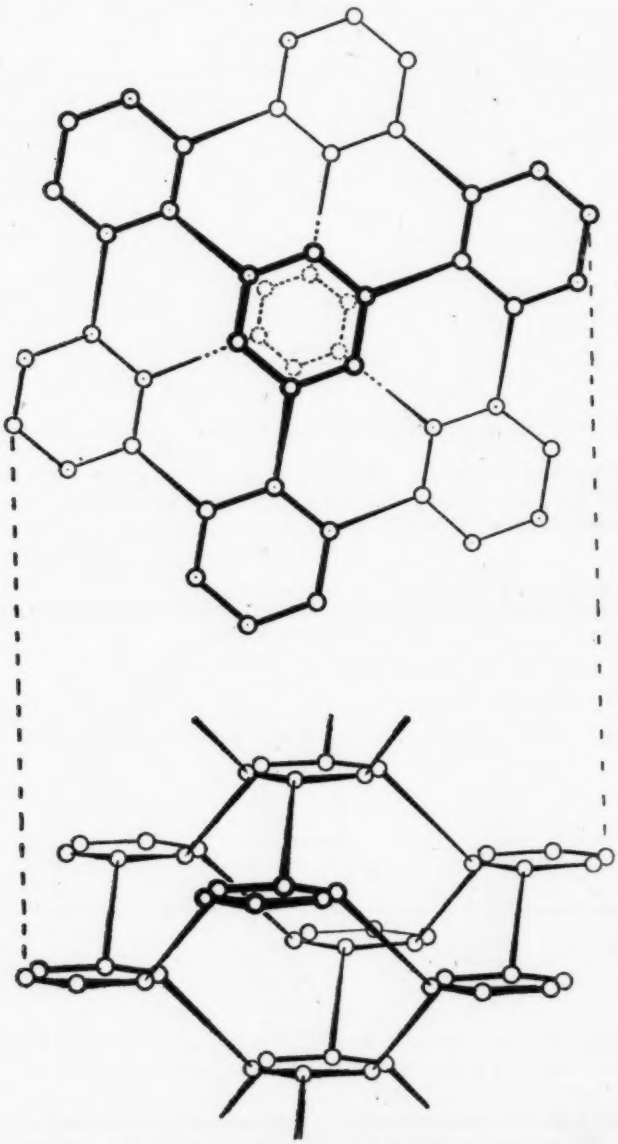


Projection of the row of molecules along the larger diagonal of Fig. 11 *in plane through this diagonal and perpendicular to the* c *face.*

shows a very large central space which is occupied to only an insignificant extent by the atoms of the benzene ring hexagons of side *ca.* 1·4 A. that should be imagined on each of the sloping lines representing the O . . O axis of one molecule. There are gaps on each face of the cage and these are so large that it is possible to insert a second identical framework structure. This is displaced vertically half-way between the top and bottom oxygen hexagons of Fig. 13, and the two frameworks make a multiple interpenetration without any closer approach of the two

independent but inseparable giant molecules than that usual for unlinked atoms. Owing to the difficulty of representing this by a perspective drawing it is shown stereoscopically in Fig. 14. In the upper part of the figure, which elsewhere shows the interpenetration of two

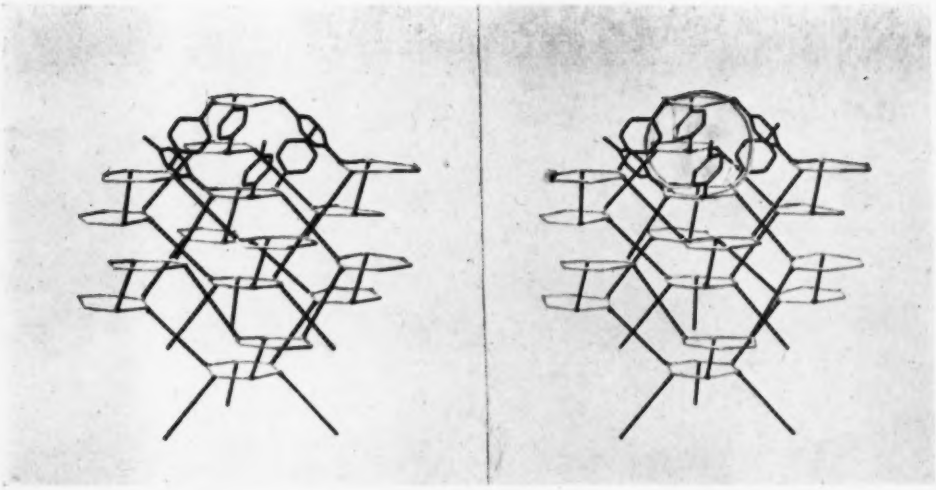
FIG. 13.



Manner of hydrogen bonding of quinol molecules. Above: In plan each regular hexagon denotes six hydrogen bonds between oxygen atoms. Hexagons at different levels are represented by different line thickness. The tapered lines, representing the O–O axis of a quinol molecule, show the method of linking to form an infinite three-dimensional cagework. Each taper points downwards from the observer. Below: Perspective drawing corresponding to above. The hexagons denote the hydrogen bonds; the longer lines connecting different hexagons denote the O–O axis of the quinol molecule.

frameworks each similar to that of Fig. 13, benzene rings have been added in the known atomic positions to show the manner of approach of the two frameworks. Although these are now separated in places at normal interatomic van der Waals distances and there are no gaps through which a molecule may easily enter or leave, there remain, between the two frameworks, cavities

FIG. 14.



Stereoscopic representation of interpenetration of two similar hydrogen-bonded cageworks each identical with that shown in Fig. 13. *Benzene rings are shown by small hexagons in the upper part of the figure but are elsewhere omitted for clarity. The larger hexagons represent the hydrogen bonds. The roughly spherical space enclosed between the two cageworks is also shown.*

[*To face p.* 220.

of sufficient size to contain a small molecule at normal unlinked distances from the surrounding atoms. Such a cavity may be seen in Fig. 14 bounded at top and bottom by oxygen hexagons of two different frameworks and at the sides by atoms of the six benzene rings shown. In this space a sphere of *ca.* 7½ A. diameter may be constructed to reach the centres of the enclosing atoms. After allowance for the contact radii of these atoms, this leaves a space, roughly spherical and of diameter 4 A., in which sulphur dioxide or another small molecule may be fitted. The number of available spaces is one for every three quinol molecules. This determines the formula of the molecular compounds mentioned above. It restricts M in $3C_6H_4(OH)_2,M$ to such molecules as may be fitted into the available space. The enclosed molecules, being trapped in the building-up of the structure during crystallation, are firmly retained so long as the quinol cagework remains unbroken but may escape when the cageworks are ruptured during solution, fusion, or grinding. Molecules small enough to escape from the cagework, *e.g.*, through the oxygen hexagons, will not form similar compounds.

The position of the sulphur dioxide molecules is determined from the electron-density maps. In the projection (Fig. 6) the molecule shows as a single peak of circular symmetry centred on the threefold axis. The vertical section (Fig. 9) shows, however, that the electron density computed for a section through the molecule does not have a maximum at the centre. In it two peaks are seen side by side and the general form of the peak, much elongated along the *c* axis, is what would be expected for a bent sulphur dioxide molecule rotating about an axis passing through or near the two oxygen atoms. The doubling of the sulphur peak then appears because the section is, in that neighbourhood, a cut through a roughly tore-shaped region of electron density produced by a sulphur atom rotating on a circle around the *c* axis. A horizontal section through the sulphur dioxide as seen in Fig. 7 gives circular contours but shows, as it should, a small decrease in electron density in the middle. Such rotations of a group of atoms in a crystal structure have been previously established in other ways, but these electron-density maps give an almost visual demonstration of the process.

The space available for rotation about a horizontal axis is restricted (see below), but it seems probable that the sulphur dioxide oxygen atoms which, if placed at $\pm 00z$ ($z = 0{\cdot}217$) would be each at 3·15 A. from the six oxygen atoms of a hydrogen-bonded OH hexagon and would act as pivots for the rotation, may undergo oscillations greater than those of the more rigidly fixed atoms of the quinol framework and in consequence do not appear as sharply resolved atoms in the vertical section through the molecule. The small deficiency in sulphur dioxide content found in analyses suggests that a number of the available holes may not be occupied. The effect of this would be to produce a lowering of the computed electron density in the regions corresponding to the sulphur dioxide.

The evidence for these vacant spaces will be considered further in a later Part dealing with other compounds of the same general formula.

It is now possible to dispose of the initial difficulties encountered in the space-group determination of this compound. The double quinol framework is itself centrosymmetric. When the spaces contain sulphur dioxide molecules, which despite their bent form are effectively centrosymmetric through rotation, the structure as a whole is centrosymmetric and has space-group $R\bar{3}$. The great similarity between *X*-ray results for " β-quinol " indicated an identical structure which at first was supposed to be that of the double framework with vacant spaces in place of the sulphur dioxide molecules. It was difficult to see how this could be non-centrosymmetric although the evidence for this is complete, but it was later shown (Palin and Powell, *loc. cit.*) that " β-quinol," which had previously been regarded as a polymorphic form of quinol obtained by crystallisation from methyl alcohol, is a compound of one molecule of methyl alcohol with three molecules of quinol. If the methyl alcohol molecules are placed with their lengths along the *c* axis, in positions similar to those of the sulphur dioxide molecules, but with all hydroxyl groups of the methyl alcohol molecules pointing towards the same end of the *c* axis, the structure is non-centrosymmetric if the methyl alcohol molecules cannot rotate about a horizontal axis, and has the space-group $R3$ as required. This direct evidence of the restriction on rotation about the horizontal axis agrees with the explanation given above of the limitation of the sulphur dioxide rotation to the vertical axis.

The authors are grateful to Messrs. I.C.I. Ltd. for the opportunity given to one of them (D. E. P.) to engage in this work.

CHEMICAL CRYSTALLOGRAPHY LABORATORY,
UNIVERSITY MUSEUM, OXFORD.

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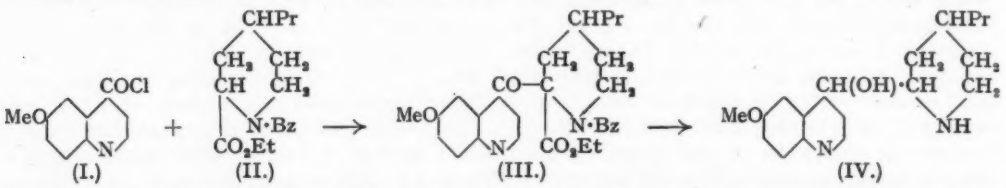
51. *The Synthesis of Antimalarial Compounds related to Niquidine. Part III. Alternative Synthesis of Dihydro-x-niquidine.*

By T. S. Work.

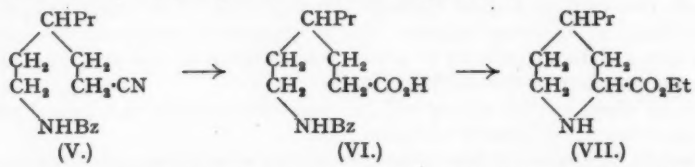
The reaction of quininic acid chloride with ethyl *N*-benzoyl-4-propylpiperidine-2-carboxylate was effected using sodium triphenylmethyl as condensing agent. The resultant keto-ester (III) was decarboxylated and reduced to give a small yield of dihydro-*x*-niquidine.

In the hope of improving upon the synthesis of dihydro-*x*-niquidine already described (Part II, *J.*, 1946, 197) trials were undertaken of the condensation of ethyl quininate with *ethyl* 3-(2-*benzamidoethyl*)*hexane*-1-*carboxylate* by the method of Ainley and King (*Proc. Roy. Soc.*, 1938, *B*, **125**, 60), but results were not encouraging.

As an alternative method the condensation of *ethyl* N-*benzoyl*-4-*propylpiperidine*-2-*carboxylate* (II) with quininic acid chloride (I) was studied (cf. Hudson and Hauser, *J. Amer. Chem. Soc.*, 1941, **65**, 3163). 4-Propylpiperidine was used as starting material for the synthesis of the desired α-carboxylate.



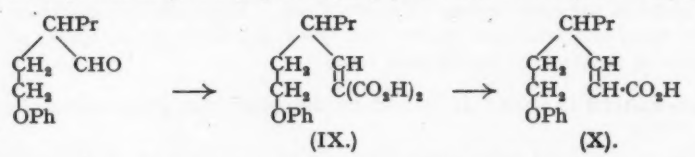
The nitrogen ring of N-*benzoyl*-4-*propylpiperidine* was opened by treatment with phosphorus pentachloride (von Braun, *Ber.*, 1906, **37**, 2916) to give benz-3-(2-chloroethyl)hexylamide. This amide was not purified but was allowed to react with potassium cyanide to yield 3-(2-*benzamidoethyl*)*hexyl cyanide* (V). The cyanide was converted into the *ester* and hydrolysed to the corresponding acid (VI) which was brominated in the α-position to the carboxyl group. Removal of the benzoyl group and cyclisation gave 4-propylpiperidine-2-carboxylic acid, isolated as the ester (VII). Benzoylation of this ester gave (II).



Ethyl *N*-benzoyl-4-propylpiperidine-2-carboxylate (II) with quininic acid chloride (I) and sodium triphenylmethyl in boiling anisole gave the keto-ester (III). This could not be purified, but on hydrolysis with dilute acid carbon dioxide was evolved and benzoic acid liberated. The resultant keto-amine was highly unstable so that it was necessary to handle it only as the hydrochloride and to reduce it as soon as possible to dihydroniquidine (IV). Despite various modifications of the conditions it was not found possible to isolate more than a trace of dihydroniquidine, and in several experiments no crystalline material was isolated.

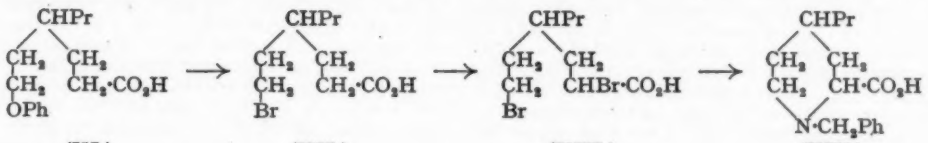
As the small yield appeared to be associated with considerable decomposition during hydrolysis of the benzamido-group, it was thought worth while to replace this by a benzyl group which could be removed by catalytic hydrogenation simultaneously with the reduction of the keto-group to a carbinol.

Phenoxyethylvaleraldehyde (Part II, *loc. cit.*) reacted readily with malonic acid to give (IX) which was decarboxylated to give 3-(2-*phenoxyethyl*)*hex*-1-*en*-1-*carboxylic acid* (X). This acid was



reduced catalytically to 3-(2-*phenoxyethyl*)*hexane*-1-*carboxylic acid* which gave a crystalline S-*benzylthiouronium* salt. Treatment of 3-(2-phenoxyethyl)hexane-1-carboxylic acid with

hydrobromic acid in acetic acid split the ether linkage, and the resultant 3-(2-*bromoethyl*)*hexane*-1-*carboxylic acid* (XII) was brominated in the α-position by treatment with bromine and phosphorus tribromide to give 1-*bromo*-3-(2-*bromoethyl*)*hexane*-1-*carboxylic acid*



(XI.) (XII.) (XIII.) (XIV.)

(XIII). The dibromo-acid reacted in the cold with benzylamine, and the resultant acid (XIV) was esterified to give the desired *ethyl* N-*benzyl*-4-*propylpiperidine*-2-*carboxylate*. The *N*-benzyl group was found to be readily removed by catalytic hydrogenation with platinum oxide at 70°.

The use of ethyl *N*-benzyl-4-propylpiperidine-2-carboxylate in place of the *N*-benzoyl ester in the sodium triphenylmethyl-catalysed reaction with quininic acid chloride did not achieve the hoped for improvement in yield in the synthesis of dihydroniquidine.

Experimental.

N-*Benzoyl*-4-*propylpiperidine*.—Propylpiperidine (43 g.) in a solution of sodium hydroxide (21 g.) was stirred vigorously and benzoyl chloride (55 g.) added slowly. The temperature was maintained below 40°. One hour after addition of benzoyl chloride the *compound* was extracted with benzene, dried, and distilled. The fraction (76·2 g.), b. p. 164—168°/0·8 mm., was collected (Found : C, 77·9; H, 9·1; N, 6·4. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·1; N, 6·1%).

3-(2-*Benzamidoethyl*)*hexyl Cyanide*.—*N*-Benzoylpropylpiperidine (94 g.) was mixed with phosphorus pentachloride (78 g.) and heated cautiously under reflux until reaction commenced. When the initial vigorous reaction had subsided the mixture was refluxed for 45 minutes. After cooling, ice was added followed by sodium hydroxide until the solution was just acid to Congo-red paper. The product was steam distilled to remove volatile by-products, and the benz-3-(2-chloroethyl)hexylamide extracted with ether. This oil (82 g.) would not crystallise and was converted into the *cyanide* without purification by heating for 14 hours with potassium cyanide (90 g.) in 75% alcohol (250 c.c.). After removal of solvent the product was extracted with ether and fractionally distilled at 0·7 mm., the fraction (67 g.), b. p. 224—226°, being collected (Found : C, 74·9; H, 8·9. $C_{16}H_{22}ON_2$ requires C, 74·4; H, 8·5%).

Ethyl 3-(2-*Benzamidoethyl*)*hexane*-1-*carboxylate*.—The cyanide from the previous experiment (67 g.) in alcohol (350 c.c.) was saturated with dry hydrogen chloride at room temperature and then boiled for 6 hours. The solvent was removed, the residue diluted with water, and the *product* extracted with ether. The oil was purified by fractional distillation, the fraction (50 g.), b. p. 214—216°/0·7 mm., being collected (Found : C, 70·8; H, 9·0; N, 4·6. $C_{18}H_{27}O_3N$ requires C, 70·8; H, 8·8; N, 4·6%).

Ethyl N-*Benzoyl*-4-*propylpiperidine*-2-*carboxylate*.—3-(2-Benzamidoethyl)hexane-1-carboxylic acid (10 g.) was obtained from the above ester (12 g.) by controlled hydrolysis with potassium hydroxide (2·6 g.) in 60% methyl alcohol (50 c.c.) at 40°. The acid, a colourless gum, was not purified but was dried over phosphoric oxide and brominated by slow addition of dry bromine (22·1 g.) to a stirred mixture of the acid and red phosphorus (1·43 g.). The flask was heated to 100° for 30 minutes to complete the reaction and the product poured on ice. The 1-bromo-3-(2-benzamidoethyl)hexane-1-carboxylic acid obtained in this way was hydrolysed by heating in a sealed tube with concentrated hydrochloric acid (25 c.c.) for 18 hours at 150°. The contents of the tube were diluted with water and benzoic acid extracted with ether. The aqueous solution of 1-bromo-3-(2-aminoethyl)hexane-1-carboxylic acid was concentrated, dried, and esterified with alcohol and dry hydrogen chloride. The acid alcohol was removed under reduced pressure and excess of sodium bicarbonate and ether were added. The solution was shaken for 1 hour to allow time for the cyclisation, and the ether was then separated and dried, and the ether-soluble oil distilled. The ethyl 4-propylpiperidine-2-carboxylate, b. p. 140—144°/18 mm. (3·3 g.), was benzoylated by the method used earlier for benzoyl-4-propylpiperidine, and the benzoate was distilled. The fraction, b. p. 190—194°/1 mm. (3·2 g.), analysed satisfactorily for *ethyl* N-*benzoyl*-4-*propylpiperidine*-2-*carboxylate* (Found : C, 71·3; H, 7·9; N, 4·8. $C_{18}H_{25}O_3N$ requires C, 71·3; H, 8·2; N, 4·6%).

Dihydro-x-*niquidine*.—The above ester (3·2 g.) in dry anisole (5 c.c.) in a dry nitrogen atmosphere was treated with a solution of one equivalent of sodium triphenylmethyl in ether. The colour of the sodium salt disappeared rapidly. Quininic acid chloride (2·3 g.) in anisole (10 c.c.) was added, and ether distilled off. The anisole solution was refluxed in a dry nitrogen atmosphere for 4 hours. The anisole was removed under reduced pressure and the residue dissolved in concentrated hydrochloric acid. Triphenylmethane was removed by extraction with ether, an equal volume of water was added to the hydrochloric acid solution, and the mixture was heated on the water-bath for 4 hours. Benzoic acid was then extracted with ether, and the hydrochloric acid solution filtered through charcoal. The acid was removed at reduced pressure below 60° and the residue dissolved in methyl alcohol and reduced catalytically using palladium–charcoal catalyst. Reduction ceased when approximately 100 c.c. of hydrogen had been adsorbed. The catalyst was removed, the solution concentrated, and the product liberated by addition of aqueous sodium carbonate. The base was extracted with chloroform, and after prolonged manipulation a small quantity of crystalline hydrobromide melting at 224° was isolated. This compound did not depress the m. p. of dihydro-*x*-niquidine (m. p. 229°) prepared by an alternative method (Part II, *loc. cit.*).

3-(2-*Phenoxyethyl*)*hexane*-1-*carboxylic Acid*.—To a solution of malonic acid (9·5 g.) and phenoxyethylvaleraldehyde (18·5 g.) (Part II, *loc. cit.*) in pyridine (40 c.c.), piperidine (0·5 g.) was added as catalyst and after 3 hours the mixture was heated on a boiling water-bath for 2 hours and finally boiled under reflux for 30 minutes. Most of the pyridine was removed under reduced pressure, the residual oil diluted with water, and excess of sodium carbonate added. Unreacted aldehyde (11·0 g.) was recovered by extraction with ether, and the unsaturated acid liberated by addition of hydrochloric acid to the alkaline solution. The acid was decarboxylated and distilled, and the fraction, b. p. 178—180°/0·7 mm., collected. The distillate (8·6 g.) was dissolved in one equivalent of 2N-sodium carbonate and reduced catalytically using palladium–strontium carbonate catalyst. The *product* was purified by distillation, and the fraction (6·3 g.), b. p. 186—188°/1 mm., collected (Found: C, 71·8; H, 8·7. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). The S-*benzylthiouronium* salt of the acid crystallised from acetone melted at 117° (Found: C, 66·9; H, 7·4; N, 6·4. $C_{15}H_{21}O_2,C_8H_{11}N_2S$ requires C, 66·4; H, 7·7; N, 6·7%). The *ethyl* ester boiled at 204°/12 mm. (Found: C, 73·8; H, 9·2. $C_{17}H_{26}O_3$ requires C, 73·4; H, 9·3%).

3-(2-*Bromoethyl*)*hexane*-1-*carboxylic Acid*.—3-(2-Phenoxyethyl)hexane-1-carboxylic acid (50 g.) in a mixture of hydrobromic acid (200 c.c.; *d* 1·7) and glacial acetic acid (560 c.c.) was boiled under reflux for 7 hours. The solvent was removed under reduced pressure and the residue diluted with water. The *bromo-acid* was extracted with ether, extracted from the ether with sodium carbonate solution, and liberated by addition of excess of hydrochloric acid. It was purified by fractional distillation, the fraction (32 g.), b. p. 164—168°/3 mm., being collected (Found: Br, 33·1. $C_9H_{17}O_2Br$ requires Br, 33·7%).

1-*Bromo*-3-(2-*bromoethyl*)*hexane*-1-*carboxylic Acid*.—The above acid (32 g.) and phosphorus tribromide (0·5 c.c.) were mixed, and dry bromine (31·5 g.) was added slowly to the stirred solution under anhydrous conditions. When addition was complete the mixture was heated and maintained at 75° for 15 hours. The temperature was finally raised to 110° for 10 minutes and the product distilled, the fraction, b. p. 180—190°/3 mm., being collected. Redistillation gave the required *acid* (46 g.), b. p. 144—146°/0·6 mm. (Found: C, 34·4; H, 5·2; Br, 49·5. $C_9H_{16}O_2Br_2$ requires C, 34·2; H, 5·1; Br, 50·6%).

Ethyl N-*Benzyl*-4-*propylpiperidine*-2-*carboxylate*.—The bromo-acid from the above experiment (40 g.) was mixed with methyl alcohol (40 c.c.), cooled in ice, and benzylamine (40 g.) in methyl alcohol (40 c.c.) added slowly. After 2 hours at 0° and 24 hours at room temperature the mixture was heated for 3 hours at 90°. Methyl alcohol was removed and the product shaken with ether and excess of dilute sodium hydroxide. The sodium *N*-benzylpropylpiperidine-2-carboxylate was sparingly soluble in sodium hydroxide, but dissolved on adding sufficient water. The ether was separated and discarded. On addition of excess of 50% sodium hydroxide to the aqueous solution the sodium salt separated and was extracted with butyl alcohol. The butyl alcohol extract was concentrated and the residue esterified by treatment with alcohol and dry hydrogen chloride. The *ethyl* N-*benzyl*-4-*propylpiperidine*-2-*carboxylate* was fractionally distilled twice, and the fraction (9·4 g.), b. p. 174—176°/1 mm. collected (Found: C, 75·2; H, 9·2; N, 5·1. $C_{18}H_{27}O_2N$ requires C, 74·7; H, 9·3; N, 4·8%).

Ethyl 4-*Propylpiperidine*-2-*carboxylate*.—The distillate from the above preparation (6·0 g.) in glacial acetic acid (50 c.c.) was reduced catalytically at 70° and normal pressure with Adams's platinum oxide catalyst. Reduction was complete in 6 hours. The catalyst was removed, the solvent distilled at reduced pressure, and the base liberated by addition of saturated sodium carbonate solution. The *base* after fractional distillation had b. p. 140—142°/18 mm. (2·5 g.) (Found: C, 66·4; H, 10·4; N, 7·2. $C_{11}H_{21}O_2N$ requires C, 66·3; H, 10·5; N, 7·0%).

I wish to thank Mr. N. Schunman for valuable technical assistance. Dr. E. R. Buchman (private communication) has successfully applied the sodium triphenylmethyl method in similar condensations of ethyl *N*-benzoylpiperidine-2-carboxylate with aromatic esters and reports equally disappointing yields. I am greatly indebted to Mr. Solomon of the Wellcome Research Institution, who developed the same method independently, for advice on the experimental technique.

National Institute for Medical Research,
London, N.W.3.

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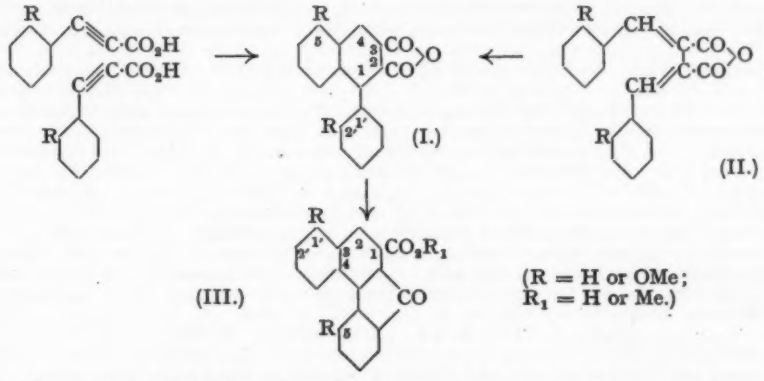
52. *Phenylpropiolic Acids. Part I. The Dimerisation of o-Methoxyphenylpropiolic Acid.*

By Fawzy Ghali Baddar.

o-Methoxyphenylpropiolic acid dimerises when heated with acetic anhydride or acetyl chloride to 2′:5-*dimethoxy*-1-*phenylnaphthalene*-2:3-*dicarboxylic anhydride* (I; R = OMe). This is converted by aluminium chloride in nitrobenzene into 1′:5-*dimethoxy*-3:4-*benzfluorenone*-1-*carboxylic acid* (III; R = OMe, R_1 = H), which is decarboxylated to 1′:5-*dimethoxy*-3:4-*benzfluorenone*. The acid from (I; R = OMe)) gives on decarboxylation 2′:5-*dimethoxy*-1-*phenylnaphthalene* which is demethylated to 2′:5-*dihydroxy*-1-*phenylnaphthalene*.

Phenylpropiolic acid is converted by acetic anhydride or phosphorus oxychloride into 1-phenylnaphthalene-2:3-dicarboxylic anhydride (I; R = H), the structure of which was established by Stobbe (*Ber.*, 1907, **40**, 3372) and Bucher (*J. Amer. Chem. Soc.*, 1908, **30**, 1244). The latter author has obtained similar products from substituted phenylpropiolic acids (cf. Haworth and Sheldrick, *J.*, 1935, 636; Haworth and Kelly, *J.*, 1936, 745) and has claimed that

2-phenylnaphthalene derivatives can also be formed under other conditions, but no experimental details have been recorded.



In the present investigation *o*-methoxyphenylpropiolic acid, prepared by refluxing 1 : 2-dibromo-2-(*o*-methoxyphenyl)propionic acid with alcoholic potassium hydroxide (cf. Perkin, *J.*, 1881, **39**, 409; Reimer and Howard, *J. Amer. Chem. Soc.*, 1928, **50**, 196), was refluxed with acetic anhydride or acetyl chloride to give a product which was proved, by molecular-weight determination, to be a dimer of the phenylpropiolic acid. Furthermore, it was shown to be the anhydride of an *o*-dibasic acid from the following facts: (1) When fused with potassium hydroxide it gave a dibasic acid which recyclised completely to the anhydride on melting or on mere boiling with acetic anhydride. (2) When heated with ammonium carbonate it was converted into the corresponding imide (cf. Schaarschmidt and Korten, *Ber.*, 1918, **51**, 1081). This excludes the possibility that the dimer is a 2-phenylnaphthalene derivative. It cannot be, however, a *cyclo*butadiene derivative (cf. Manthey, *Ber.*, 1900, **33**, 3081), for the solution of its acid in sodium hydrogen carbonate failed to discharge the colour of potassium permanganate solution (cf. Bucher, *loc. cit.*).

It appears, therefore, that the dimer must be 2′ : 5-*dimethoxy*-1-*phenylnaphthalene*-2 : 3-*dicarboxylic anhydride* (I; R = OMe). This is rigidly established by the fact that the same anhydride is obtained by the action of light or heat on di-(*o*-methoxybenzylidene)succinic anhydride (II; R = OMe) (unpublished work by F. G. Baddar and Munir Gindy; cf. Stobbe, *loc. cit.*; Bucher, *loc. cit.*).

The acid from (I; R = OMe) gave on decarboxylation 2′ : 5-*dimethoxy*-1-*phenylnaphthalene*, which was demethylated to 2′ : 5-*dihydroxy*-1-*phenylnaphthalene*. The latter on being distilled with zinc dust gave a viscous oil from which no pure nitro-derivative of 1-phenylnaphthalene could be obtained (cf. Haworth and Sheldrick, *loc. cit.*). This may be due to the contamination of the product with fluoranthene resulting from 2′ : 5-dihydroxy-1-phenylnapthalene during zinc dust distillation. The anhydride (I; R = OMe) was converted by aluminium chloride in nitrobenzene into 1′ : 5-dimethoxy-3 : 4-benzfluorenone-1-carboxylic acid (III; R = OMe, R_1 = H). The reaction was incomplete if carried out in cold or hot carbon disulphide or benzene instead of nitrobenzene (cf. Schaarschmidt, *loc. cit.*). This acid was decarboxylated to 1′ : 5-*dimethoxy*-3 : 4-*benzfluorenone*. Similarly, *p*-nitro- and *p*-methoxy-phenylpropiolic acids dimerised when refluxed with acetic anhydride; the product from the former was proved to be a 1-phenylnaphthalene derivative, that from the latter is under investigation (unpublished work by F. G. Baddar and Lanson Salib El-Assal).

Experimental.

(M. p.'s are not corrected. Microanalyses were carried out by Drs. Weiler and Strauss of Oxford.)

cis-o-*Methoxycinnamic Acid.*—This was prepared according to Stoermer and Friemel (*Ber.*, 1911, **44**, 1843) but by using 50 g. of sodium hydroxide instead of 30 g., and hydrolysing the ether ester directly by refluxing for 30—45 minutes. The alkaline solution was extracted with ether, and the aqueous layer (charcoal) filtered and acidified. The acid was freed from unchanged coumarin by dissolving it in sodium carbonate solution. On crystallisation from dilute alcohol, *cis-o*-methoxycinnamic acid was obtained in colourless cubes, m. p. 94—95° (Stoermer and Friemel, and Reimer and Howard, *locc. cit.*, give m. p.'s 88—89° and 92—93° respectively; yield about 90%).

1 : 2-*Dibromo*-2-(*o-methoxyphenyl*)*propionic Acid.*—A cold solution of pure *cis-o*-methoxycinnamic acid (120 g.; 1 mol.) in carbon tetrachloride (600 c.c.) was brominated with bromine (36 c.c., 1 mol.) in 120 c.c. of carbon tetrachloride (cf. *Org. Synth.*, XII, 36). The precipitated bromination product was

filtered off and washed with carbon tetrachloride. The crude product (*ca.* 200—220 g.) shrank at about 130° and had m. p. 160—165°. This was purified by crystallisation from benzene; the first crop melted at 165—170° (*ca.* 120 g.) and a further crop, precipitated on concentration, melted indefinitely between 130° and 160° (*ca.* 50—60 g.). This was probably a mixture of the two dibromo-acids isolated by Reimer and Howard (*loc. cit.*). The two crops, however, were mixed together and subjected to the following treatment.

o-*Methoxyphenylpropiolic Acid.*—A powdered mixture of the above crystallised acids (180 g.) was added to cold 20% alcoholic potassium hydroxide (700 c.c.), and the mixture heated under reflux for 6 hours and worked up as usual (cf. *Org. Synth.*, XII, 60). The acid was best purified by dissolving it in ether and re-extracting it from the solution by sodium carbonate. On crystallisation from benzene *o*-methoxyphenylpropiolic acid separated in colourless crystals, m. p. 128—129° (yield about 50%). When twice crystallised from benzene, it was obtained in aggregates of monoclinic crystals, m. p. 120—130° (Found: C, 68·1; H, 4·6. Calc. for $C_{10}H_8O_3$: C, 68·2; H, 4·6%); Perkin (*loc. cit.*) and Reimer and Howard (*loc. cit.*) give m. p.'s 124—126° and 125°, respectively.

2′ : 5-*Dimethoxy*-1-*phenylnaphthalene*-2 : 3-*dicarboxylic Anhydride* (I; R = OMe).—*o*-Methoxyphenylpropiolic acid (20 g.) was refluxed with acetic anhydride (60 c.c.) for 3 hours, and the precipitated pure anhydride filtered off and washed with ether (yield 85%). It melted at 244—245° and was pure enough for the following steps. On crystallisation from glacial acetic acid the *anhydride* separated in straw-yellow, tabular, prismatic crystals, m. p. 245—246° [Found: C, 71·8; H, 4·2; OCH_3, 18·5; *M* (Rast), 346. $C_{20}H_{14}O_5$ requires C, 71·8; H, 4·2; OCH_3, 18·6%; *M*, 334].

Methyl 1′ : 5-*Dimethoxy*-3 : 4-*benzfluorenone*-1-*carboxylate* (III; R = OMe, R_1 = Me).—Nitrobenzene (180 c.c.) was cooled with stirring to − 5° and a finely powdered mixture of the anhydride (I; R = OMe) (15 g.) and aluminium chloride (75 g.) was slowly added during an hour. The whole was kept at 0° for 2—3 hours, then allowed to stand at room temperature (20—30°) for 3 days with occasional stirring. The brownish-green product was poured on ice, acidified, and the nitrobenzene removed by steam-distillation. The product was dissolved in hot ammonium hydroxide, filtered, and precipitated. The dry crude acid (yield, 12 g.), being difficultly soluble in most organic solvents, was directly esterified by refluxing it with a mixture of methyl iodide (60 g.), acetone (500 c.c.), and dry potassium carbonate (40 g.) for 4 hours. The acetone was removed, and the solution of the ester in benzene was washed with sodium hydroxide solution. The *methyl* ester was best purified by crystallisation from dioxan and then from alcohol–dioxan or alcohol, giving red prismatic needles, m. p. 190·5—191·5° [Found: C, 72·5; H, 4·6; *M* (Rast), 348. $C_{21}H_{16}O_5$ requires C, 72·4; H, 4·6%; *M*, 348]; yield, 7 g. (*ca.* 54%). The free acid (III; R = OMe, R_1 = H) was obtained by hydrolysing the ester with alcoholic potassium hydroxide; it crystallised with difficulty from benzene or toluene in reddish-brown needles, m. p. 258—259°.

1′ : 5-*Dimethoxy*-3 : 4-*benzfluorenone.*—1′ : 5-Dimethoxy-3 : 4-benzfluorenone-1-carboxylic acid (1 g.) and copper bronze (0·12 g.) were refluxed in quinoline (10 c.c.) for ½ hour. The benzene solution was repeatedly extracted with hydrochloric acid, then washed with sodium hydroxide solution. On crystallisation from dilute acetic acid and then dioxan–alcohol, 1′ : 5-*dimethoxy*-3 : 4-*benzfluorenone* was obtained in red prismatic needles, m. p. 176° (Found: C, 78·5; H, 4·88; OCH_3, 19·2; *M*, 282. $C_{19}H_{14}O_3$ requires C, 78·6; H, 4·86; OCH_3, 21·4%; *M*, 290).

2′ : 5-*Dimethoxy*-1-*phenylnaphthalene*-2 : 3-*dicarboxylic Acid.*—The powdered anhydride (I; R = OMe) (5 g.) was added to molten potassium hydroxide (15 g.) and stirred at 200—210° for about 20 minutes. The ice-cold aqueous extract gave on acidification 2′ : 5-dimethoxy-1-phenylnaphthalene-2 : 3-dicarboxylic acid; yield, *ca.* 80%. On crystallisation from acetic acid it was partly converted into the anhydride. It melted at 245—246° being transformed into the anhydride. It was easily converted into the anhydride on being boiled with acetic anhydride for 1—2 minutes. The acid was best identified as its *methyl* ester which was prepared by treating a dioxan solution of the acid with diazomethane in ether. On crystallisation from benzene–light petroleum (b. p. 60—70°), this ester separated in colourless crystals, m. p. 133—134° (Found: C, 69·5; H, 5·3; OCH_3, 30·7; *M*, 368. $C_{22}H_{20}O_6$ requires C, 69·5; H, 5·3; OCH_3, 32·6%; *M*, 380).

2′ : 5-*Dimethoxy*-1-*phenylnaphthalene.*—A stirred mixture of 2′ : 5-dimethoxy-1-phenylnaphthalene-2 : 3-dicarboxylic acid (13 g.), quinoline (40 c.c.), and copper bronze (2·6 g.) was slowly heated during ½ hour to 200°. The temperature was kept at 200—210° and a further amount of copper bronze (2·6 g.) was added during 2 hours, and stirring and heating continued for a further hour. The reaction mixture was poured into dilute hydrochloric acid, and the precipitated solid was filtered off, dried, and thoroughly extracted with ether or benzene. The solution was washed with sodium hydroxide and the viscous yellow-brown oil obtained on vacuum distillation, b. p. 190—200°/5 mm. (yield, 40%), gave on repeated crystallisation from methyl or ethyl alcohol 2′ : 5-*dimethoxy*-1-*phenylnaphthalene* in colourless aggregates of monoclinic crystals, m. p. 95—96° [Found: C, 81·3; H, 6·1; OCH_3, 19·0; *M* (Rast), 250. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1; OCH_3, 23·5%; *M*, 264]. The dilute alcoholic solution showed a strong blue fluorescence. The sodium hydroxide extract, on acidification, precipitated a mono-carboxylic acid which gave on crystallisation from benzene–light petroleum (b. p. 60—70°) 2′ : 5-*dimethoxy*-1-*phenylnaphthalene*-2 (or 3)-*carboxylic acid* in pale yellow prisms, m. p. 229·5—230·5° (Found: C, 74·4; H, 5·2; *M*, 308. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·3%; *M*, 308). Its *methyl* ester, prepared by diazomethane, crystallised from alcohol in yellow flakes, m. p. 165·5—166·5° [Found: C, 74·5; H, 5·7; *M* (Rast), 326. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%; *M*, 322].

2′ : 5-*Dihydroxy*-1-*phenylnaphthalene.*—The dimethyl ether (4 g.) was refluxed with a mixture of glacial acetic acid (60 c.c.) and hydriodic acid (30 c.c.; *d* 1·96) for 5 hours. The reaction mixture was diluted with sodium sulphite solution, the acetic acid neutralised with sodium carbonate, and the product extracted with ether. The ethereal solution was extracted with alkali, and the precipitated phenol re-extracted with ether (yield, 2·7 g.). On crystallisation from benzene 2′ : 5-*dihydroxy*-1-*phenylnaphthalene* was obtained in very pale yellow crystals, m. p. 187—188° (Found: C, 81·1; H, 5·2; active H, 0·88; *M*, 224. $C_{16}H_{12}O_2$ requires C, 81·4; H, 5·1; active H, 0·85%; *M*, 236). It gave with alcoholic ferric chloride a green solution.

1-*Phenylnaphthalene*-2 : 3-*dicarboxyimide*.—1-Phenylnaphthalene-2 : 3-dicarboxylic anhydride (4 g.) was thoroughly powdered with ammonium carbonate (7 g.), and the mixture heated on the direct flame with frequent shaking until it melted. The gentle heating was continued, the mass being kept just molten until no more ammonia was evolved. The product was washed with sodium carbonate solution, and the insoluble residue extracted with sodium hydroxide, filtered and reprecipitated with acid. On crystallisation from alcohol, the imide was obtained in colourless, silky needles, m. p. 249° (yield, 85%) (cf. Schaarschmidt and Korten, *loc. cit.*) (Found: C, 79·2; H, 4·25; N, 5·45. Calc. for $C_{18}H_{11}O_2N$: C, 79·1; H, 4·06; N, 5·1%).

2′ : 5-*Dimethoxy*-1-*phenylnaphthalene*-2 : 3-*dicarboxyimide*.—The anhydride (I; R = OMe) (1 g.) was powdered with ammonium carbonate (8 g.) and treated as above. The product (0·2 g.) crystallised from acetic acid or dioxan–alcohol to give the *imide* in colourless leaflets, m. p. 273—274° (Found: C, 71·4; H, 4·6; N, 4·55. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5; N, 4·2%).

3 : 4-*Benzfluorene*.—3 : 4-Benzfluorenone-1-carboxylic acid (0·5 g.) was distilled with zinc dust (10 g.), and the distillate was extracted with alcohol (charcoal), and then twice crystallised from methyl alcohol to give 3 : 4-benzfluorene in colourless leaflets, m. p. 126—127° (Found: C, 94·4; H, 5·6. Calc. for $C_{17}H_{12}$: C, 94·4; H, 5·6%); Cook *et al.* (*J.*, 1935, 1323) give m. p. 124—125°.

1′ : 5-Dimethoxy-3 : 4-benzfluorenone-1-carboxylic acid was prepared by Munir Gindy for studying its fission with alkali. The results will be published soon.

FOUAD I UNIVERSITY, FACULTY OF SCIENCE,
CAIRO, EGYPT.

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53. *Cinnolines. Part IX. The Preparation of Some* 6 : 7- *and* 7 : 8-*Disubstituted*-4-*hydroxycinnolines.*

By J. R. KENEFORD and J. C. E. SIMPSON.

Syntheses are described, with proofs of structure, of 6-*chloro*-7-*methyl*-, 6-*bromo*-7-*methyl*-, 8-*chloro*-7-*methyl*-, 6 : 7-*dichloro*-, and 7 : 8-*dichloro*-4-*hydroxycinnoline*. *p*-Methyl-, *p*-chloro-, and 3 : 4-dichloro-acetophenone are used as starting materials, and the preparations are illustrative of the general method of 4-hydroxycinnoline synthesis from *o*-aminoacetophenones previously developed (*J.*, 1945, 520).

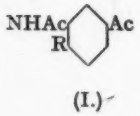
As part of an investigation of the uses of the cinnoline nucleus for the synthesis of antimalarial agents, we have prepared a variety of 6- and 8-substituted 7-chloro- and 7-methyl-4-hydroxycinnolines from appropriate *o*-aminoacetophenones by the method previously described (*J.*, 1945, 520). The present paper describes the preparation of these cinnolines and the intermediate amino-ketones starting from *p*-methyl-, *p*-chloro-, and 3 : 4-dichloro-acetophenone.

Nitration of *p*-methylacetophenone gives 3-nitro-4-methylacetophenone (Errera, *Gazzetta*, 1891, **21**, 92; Ganguly and Le Fèvre, *J.*, 1934, 852), the orientation of which was established, according to Ganguly and Le Fèvre (*loc. cit.*), by oxidation to 3-chloro-4-methylbenzoic acid *via* 3-chloro-4-methylacetophenone. In view of the fact that no experimental details of this oxidation are recorded (although details are given of oxidations which do not furnish proof of orientation), it may be pointed out that the transformations described below constitute proof of orientation independent of reference compounds.

3-Nitro-4-methylacetophenone on reduction and acetylation gave 3-*acetamido*-4-*methylacetophenone* (I; R = Me), nitration of which gave all three possible mono-nitro compounds. Of these, 3-*nitro*-5-*acetamido*-4-*methylacetophenone* (II) was formed only in small amount (3·5%), and its formation could be suppressed completely under suitable conditions; it was, as expected, more basic than the *o*- and *p*-nitroacetamido-compounds. Its constitution was proved by hydrolysis to 3-*nitro*-5-*amino*-4-*methylacetophenone* (III) and deamination of the latter to 3-nitro-4-methylacetophenone. The remaining nitroacetamidomethylacetophenones, which formed the bulk of the nitration product (the *p*-nitroacetamido-compound predominating), could not usually be separated by crystallisation, although on one occasion an apparently pure specimen of 2-*nitro*-5-*acetamido*-4-*methylacetophenone* (IV; R = Me) was obtained by crystallisation from alcohol. Acid hydrolysis of the mixed products gave a mixture of 2-*nitro*-5-*amino*- (V; R = Me) and 2-*nitro*-3-*amino*-4-*methylacetophenone* (VI; R = Me), readily separated by use of the appropriate solvents. The orientation of the latter was proved by reduction and conversion into the *phenazine* (VII; R = Me). Additional proof of orientation, showing that the *C*-acetyl and nitro-groups occupy *o*-positions in (VI; R = Me), was obtained by conversion of this substance into 3-*chloro*-2-*nitro*-4-*methylacetophenone* (VIII; R = Cl), from which 8-*chloro*-4-*hydroxy*-7-*methylcinnoline* (IX; R_1 = H, R_2 = Cl) was prepared by reduction and diazotisation; 3-*bromo*-2-*nitro*-4-*methylacetophenone* (VIII; R = Br) was also prepared from (VI; R = Me). The orientation of (V; R = Me) follows from the establishment

of the structures of (III) and (VI; R = Me); in agreement with this constitution, no phenazine could be obtained from the reduction product of (V; R = Me). The constitution of the substance as an *o*-nitroacetophenone was independently proved by its conversion into 6-*chloro*- and 6-*bromo*-4-*hydroxy*-7-*methylcinnoline* (IX; R_1 = Cl or Br, R_2 = H) *via* 5-*chloro*- and 5-*bromo*-2-*nitro*-4-*methylacetophenone* (X; R_2 = Me, R_1 = Cl or Br) by reduction and diazotisation. In contrast to that of the chloro-cinnoline, the formation of the bromo-cinnoline (IX; R_1 = Br, R_2 = H) did not proceed smoothly, and was accompanied by the production of much steam-volatile material. This consisted chiefly of 5-*bromo*-2-*hydroxy*-4-*methylacetophenone* (XI; R = OH), together with small amounts of a non-phenolic ketone which was not identified, but was apparently not 3-bromo-4-methylacetophenone (XI; R = H).

The fact that two isomeric chloro-4-hydroxy-7-methylcinnolines have been prepared from *p*-methylacetophenone by this series of reactions furnishes the confirmatory proof, referred to above, that nitration of this ketone gives 3-nitro-4-methylacetophenone; had nitration occurred in the 2-position, only one *o*-nitro-ketone, and hence only one cinnoline, could have been obtained from the resultant acetamido-methylacetophenone.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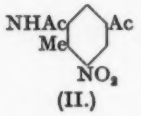
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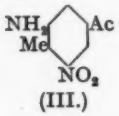
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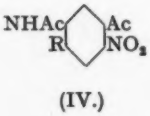
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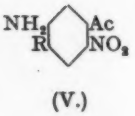
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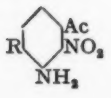
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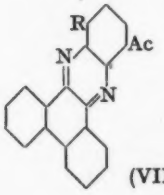
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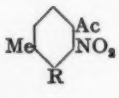
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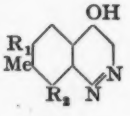
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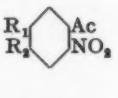
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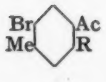
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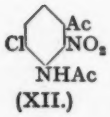
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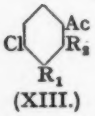
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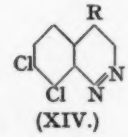
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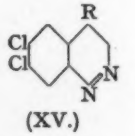
(XV.)

The preparation of the cinnolines from *p*-chloroacetophenone followed similar general lines. The nitration of the ketone to 4-chloro-3-nitroacetophenone has been described by Mayer, Stark, and Schön (*Ber.*, **1932**, **65**, 1333), who oriented the compound by oxidation to 4-chloro-3-nitrobenzoic acid. In agreement with this result, we observed that this chloronitro-acetophenone gives a depression in m. p. when mixed with 4-chloro-2-nitroacetophenone of proved structure (following paper). Reduction and acetylation furnished 4-*chloro*-3-*acetamido-acetophenone* (I; R = Cl), nitration of which gave a mixture of 4-*chloro*-2-*nitro*-5- (IV; R = Cl) and -3-*acetamidoacetophenone* (XII). In contrast to the nitration of (I; R = Me), *m*-nitration of (I; R = Cl) (with reference to the *C*-acetyl group) did not occur to any appreciable extent; however, it is probable that this difference is due to experimental rather than to constitutional factors, because the formation of 3-nitro-5-acetamido-4-methylacetophenone is itself dependent on the conditions of nitration (see Experimental), and it has also been observed (this vol., p. 238), in the nitration of *o*-acetamidoacetophenone, that the size of the batch and the speed of admixture of reactants can influence the result considerably.

The structure of (XII) followed from its hydrolysis to the *nitro-amine* (VI; R = Cl), reduction of the latter, and conversion into the phenazine (VII; R = Cl), identical with the compound prepared (following paper) from 4-chloro-3-nitro-2-aminoacetophenone (XIII; R_1 = NO_2, R_2 = NH_2). Diazotisation of (VI; R = Cl) in hydrochloric acid followed by a Sandmeyer reaction gave only 2 : 3 : 4-*trichloroacetophenone* (XIII; R_1 = R_2 = Cl), but the use of sulphuric acid as diazotisation medium afforded 3 : 4-*dichloro*-2-*nitroacetophenone* (XIII; R_1 = Cl, R_2 = NO_2) in moderate yield, from which 7 : 8-*dichloro*-4-*hydroxycinnoline* (XIV; R = OH) was prepared by reduction, diazotisation, and ring-closure. By successive chlorination and phenoxylation, this substance was converted into 4 : 7 : 8-*trichlorocinnoline* (XIV; R = Cl) and 7 : 8-*dichloro*-4-*phenoxycinnoline* (XIV; R = OPh).

Hydrolysis of (IV; R = Cl) gave the free *amine* (V; R = Cl), and deamination yielded

4-chloro-2-nitroacetophenone (XIII; $R_1 = H$, $R_2 = NO_2$), thus (in view of the foregoing evidence) establishing its orientation. Diazotisation of (V; R = Cl), followed by the appropriate Sandmeyer reaction, furnished 4 : 5-dichloro-2-nitroacetophenone (X; $R_1 = R_2 = Cl$), identical with the compound obtained by nitrating 3 : 4-dichloroacetophenone (XIII; $R_1 = Cl$, $R_2 = H$). This nitration, originally* carried out by Roberts and Turner (*J.*, 1927, 1832), is stated by them to yield 3 : 4-dichloro-2-nitroacetophenone; this appears to be due to an error in nomenclature, as the work described by Roberts and Turner makes it clear that their compound is in reality 4 : 5-dichloro-2-nitroacetophenone; however, it seemed desirable to have independent proof of orientation (especially as 4 : 5-dichloro-2-nitroacetophenone is much more readily prepared from 3 : 4-dichloroacetophenone than from *p*-chloroacetophenone), and this has now been provided by the above identification. Reduction of this substance to 4 : 5-dichloro-2-aminoacetophenone, and diazotisation of the latter, gave 6 : 7-*dichloro*-4-*hydroxycinnoline* (XV; R = OH), which was converted by standard methods into 6 : 7-*dichloro*-4-*acetoxy*-, 4 : 6 : 7-*trichloro*-, and 6 : 7-*dichloro*-4-*phenoxy-cinnoline* (XV; R = OAc, Cl, and OPh).

Experimental.

Melting points are uncorrected. Nitrations were carried out with mechanical stirring. Nitro-amines were prepared from nitro-acetamido-compounds by refluxing for ½ hour with hydrochloric acid (6N, 5—7 parts by vol.) and isolated by basification with ammonia. Sandmeyer reactions were carried out by adding the diazonium to the cuprous solution in portions at room temperature, followed by heating for ½—1 hour at 70°; products were isolated by ether extraction, the extracts being washed successively with acid, sodium hydroxide, and water. 4-Hydroxycinnolines were prepared by heating the diazonium solutions at 70—90° until the coupling reaction with alkaline β-naphthol was negative or negligible (1—2 hours); they separated directly or were isolated by dilution with water. Unless otherwise specified in the text, the following statements apply: (i) Compounds were crystallised from alcohol. (ii) The ligroin used had b. p. 60—80°. (iii) Nitro-compounds were reduced to amines by heating (1 part) at 95° in acetic acid (7—8 vols.) with gradual addition of iron powder (1·5 parts) and water (7—8 vols.) (cf. *J.*, 1945, 646), and isolated by ether extraction.

3-*Nitro*-4-*methylacetophenone*.—This was prepared by the method of Ganguly and Le Fèvre (*loc. cit.*), using 110-g. batches of *p*-methylacetophenone, 740 c.c. of nitric acid (*d* 1·5), and a time of addition of 1—1½ hours, the temperature being maintained below 0°. The clear solution was stirred for a further ½ hour and then poured on crushed ice (*ca.* 2 kg.). The nitro-ketone had m. p. 60—62° after one crystallisation (average yield from 9 runs, 82%).

3-*Acetamido*-4-*methylacetophenone*.—The following modification of the method of Ganguly and Le Fèvre (*loc. cit.*) gave an improved yield. A solution of 3-nitro-4-methylacetophenone (100 g.) in alcohol (400 c.c.) was treated with iron powder (102 g.) and hydrochloric acid (28 c.c., 6N). The well-stirred suspension was refluxed for 1½ hours, more acid (28 c.c.) cautiously added, and heating continued for a further 1½ hours. A third 28 c.c. portion of acid was added, followed by 2 hours' heating. The suspension was then filtered, the sludge washed with hot alcohol (200 c.c.) containing concentrated hydrochloric acid (5 c.c.), and the filtrate and washings concentrated under reduced pressure to approximately 100 c.c. The residue was then basified with dilute ammonia and extracted with ether. Evaporation of the washed and dried extract yielded the crude amine as a dark brown oil which crystallised slowly on standing. Acetic anhydride (206 c.c.) was added, and the mixture heated on the steam-bath for 1 hour. 3-*Acetamido*-4-*methylacetophenone* separated from the reaction mixture in soft, cream-coloured needles, m. p. 143—144°, and more was obtained by decomposition of the filtrate (average yield from 10 runs, 73% based on nitro-compound); the m. p. was unchanged after crystallisation (Found: C, 69·05; H, 6·9. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·9%).

Nitration of 3-*Acetamido*-4-*methylacetophenone*.—(*a*) The foregoing compound (40 g.) was added during 1 hour to a mixture of nitric acid (*d* 1·495) and concentrated sulphuric acid (220 c.c., 5 : 2 by volume) at − 15° to − 10°. After a further ½ hour the solution was poured on crushed ice, and the mixture of nitro-compounds (A) filtered off. Basification of the filtrate (ammonia) and extraction with ether gave a crystalline residue which yielded 3-*nitro*-5-*acetamido*-4-*methylacetophenone* in clusters of small, colourless needles, m. p. 200—200·5° (Found: C, 56·5; H, 5·4; N, 11·85. $C_{11}H_{12}O_4N_2$ requires C, 55·9; H, 5·1; N, 11·9%). 3-*Nitro*-5-*amino*-4-*methylacetophenone* formed long, feathery, reddish-brown needles, m. p. 158—159·5° (Found: C, 55·7; H, 5·3; N, 15·1. $C_9H_{10}O_3N_2$ requires C, 55·6; H, 5·2; N, 14·4%). Deamination of this substance was effected by addition of amyl nitrite (2 c.c.) to a solution of it (0·5 g.) in alcohol (100 c.c.) and concentrated sulphuric acid (8 c.c.); the solution was heated to boiling on the steam-bath during 5 minutes, boiled for a short time, made alkaline with solid sodium bicarbonate, and partly freed from alcohol (reduced pressure). The product was isolated by ether extraction, and yielded 3-nitro-4-methylacetophenone (0·3 g.), m. p. 60—61°, from ligroin, not depressed by admixture with authentic material.

No pure substance could be isolated from the mixture (A), which was therefore hydrolysed, although in one small-scale experiment (from 8 g. of 3-acetamido-4-methylacetophenone) direct crystallisation

* *Added in Proof*.—Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 405) state that they were unable to reproduce this result. In our experience, the experiment of Roberts and Turner is reproducible, and the nitration has been carried out many times under the more precise conditions which we describe in the Experimental. We would also point out that the compound, m. p. 176—177° (corr.), which Leonard and Boyd, on a conjectural basis, formulate as 4-chloro-2-nitro-5-acetamidoacetophenone, is clearly that which we have proved to be 4-chloro-2-nitro-3-acetamidoacetophenone.

afforded *2-nitro-5-acetamido-4-methylacetophenone* as large, lemon-yellow rhombohedra, m. p. 164—165° (yield, 35%) (Found: C, 56·3; H, 4·95; N, 12·2. $C_{11}H_{12}O_4N_2$ requires C, 55·9; H, 5·1; N, 11·9%), identified by hydrolysis to the amine described below.

(*b*) On a larger scale, the acetamido-ketone (80 g.) was added during ½ hour to a mixture of nitric acid (315 c.c., *d* 1·492) and concentrated sulphuric acid (126 c.c.) at 0—10°. After a further ½ hour at the same temperature, the solution was poured on ice (2 kg.); the average yield of crude nitration product from eight runs was 54·6 g. (55%) (variations of these conditions in small-scale trials did not lead to substantially higher yields). The acid filtrates were basified and extracted with ether, but only a small quantity of oily product resulted. The mixed nitro-compounds (in 100-g. batches) were hydrolysed to the nitro-amines (428 g.). Crystallisation gave *2-nitro-5-amino-4-methylacetophenone* as glistening bronze plates, m. p. 186—187° (230 g., 35%) (Found: C, 55·65; H, 5·45. $C_9H_{10}O_3N_2$ requires C, 55·6; H, 5·2%). Reduction of this substance gave a crystalline product, m. p. 175—180° (depressed by admixture with the nitro-amine), which gave no phenazine on attempted condensation with phenanthraquinone.

The alcoholic filtrates from the foregoing nitro-amine, freed as completely as possible from this substance, were concentrated further, and the residue crystallised from methyl ethyl ketone; *2-nitro-3-amino-4-methylacetophenone* was thus obtained in gross, orange prisms, m. p. 102·5—103·5° (Found: C, 55·65; H, 5·35; N, 14·35. $C_9H_{10}O_3N_2$ requires C, 55·6; H, 5·2; N, 14·4%). A solution of the substance (0·3 g.) in acetic acid (6·5 c.c.) was reduced at 95° with iron filings (0·8 g.) and water (6·5 c.c.). The diamine, isolated in the known manner, had m. p. 75—85° (depressed by the starting material), and when it (0·15 g.) was refluxed with phenanthraquinone (0·21 g.) in alcohol (30 c.c.), the *phenazine* rapidly separated (small, soft, yellow needles, m. p. 289—290°, from acetic acid) (Found: C, 81·65; H, 5·0; N, 8·45. $C_{22}H_{16}ON_2$ requires C, 82·1; H, 4·8; N, 8·3%).

5-Chloro-2-nitro-4-methylacetophenone.—The finely-divided suspension obtained by rapid cooling of a hot solution of 2-nitro-5-amino-4-methylacetophenone (15 g.) in hydrochloric acid (300 c.c. of 9N) was diazotised with aqueous sodium nitrite (10%, 55 c.c.), and added to cuprous chloride (from 24 g. of copper sulphate crystals) in concentrated hydrochloric acid (38 c.c.). *5-Chloro-2-nitro-4-methylacetophenone* (crude yield, 15·7 g.) formed long, almost colourless, brittle needles, m. p. 71—72° (Found: C, 50·8; H, 4·0. $C_9H_8O_3NCl$ requires C, 50·6; H, 3·8%).

5-Chloro-2-amino-4-methylacetophenone.—This *amine* (yield, 97%) formed irregular yellow blades, m. p. 109—109·5° (Found: C, 58·8; H, 5·45. $C_9H_{10}ONCl$ requires C, 58·8; H, 5·5%).

6-Chloro-4-hydroxy-7-methylcinnoline.—The suspension of the hydrochloride of the foregoing amine, obtained by cooling a hot solution of the crude base (13·1 g.) in hydrochloric acid (300 c.c., 6N), was diazotised with 10% sodium nitrite (54 c.c.). Crude *6-chloro-4-hydroxy-7-methylcinnoline* (12·5 g., m. p. 260—266°) formed micro-prisms, m. p. 271—272°, after crystallisation (Found: C, 55·55; H, 3·85; N, 14·9. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·65; N, 14·4%).

5-Bromo-2-nitro-4-methylacetophenone.—Prepared similarly to the chloro-compound, but using hydrobromic acid (*d* 1·5) throughout (diluted with 3 vols. of water for the diazotisation), this *compound* (22 g. from 25 g. of 2-nitro-5-amino-4-methylacetophenone) separated from ligroin in large, jagged, pale yellow blades, m. p. 82—83° (Found: C, 42·2; H, 3·2; Br, 31·5. $C_9H_8O_3NBr$ requires C, 41·9; H, 3·1; Br, 31·0%).

5-Bromo-2-amino-4-methylacetophenone.—This *amine* (crude yield, 95%) formed long, lustrous, amber-coloured needles, m. p. 122·5—123·5° (Found: C, 47·6; H, 4·6; N, 6·5. $C_9H_{10}ONBr$ requires C, 47·4; H, 4·4; N, 6·1%).

6-Bromo-4-hydroxy-7-methylcinnoline.—A solution of the above amine (12·5 g.) in 2N-hydrochloric acid (200 c.c.) was diazotised with 10% sodium nitrite (40 c.c.); a condenser was used during the subsequent heating to retain volatile material. The crude product was digested with ether, and the insoluble residue (4·7 g.) gave *6-bromo-4-hydroxy-7-methylcinnoline* as buff-coloured micro-prisms, m. p. 273—274° (Found: C, 45·15; H, 3·0; N, 12·0. $C_9H_7ON_2Br$ requires C, 45·2; H, 3·0; N, 11·7%).

5-Bromo-2-hydroxy-4-methylacetophenone.—The ethereal solution from the previous experiment was extracted with dilute sodium hydroxide; the alkaline solution was then acidified, and the product again taken into ether and isolated in the customary manner. The crude phenol (5·45 g.) was dissolved in hot ligroin, from which *5-bromo-2-hydroxy-4-methylacetophenone* separated in long, pale yellow needles, m. p. 86—87° (Found: C, 47·7; H, 4·1. $C_9H_9O_2Br$ requires C, 47·2; H, 4·0%). The *benzoyl* derivative (Schotten–Baumann conditions) formed colourless, glistening rhombohedra, m. p. 95·5—96·5° (Found: C, 57·65; H, 4·2. $C_{16}H_{13}O_3Br$ requires C, 57·7; H, 3·9%).

The foregoing ethereal solution, after being freed from phenolic material, was washed with water, dried, and evaporated, yielding a red mobile oil (0·95 g.) which crystallised on standing. This material gave an oxime, m. p. 132—135°, and a semicarbazone, m. p. 290—300° (decomp.), under the usual conditions.

3-Bromo-4-methylacetophenone.—Acid hydrolysis of 3-acetamido-4-methylacetophenone gave the amine as a slowly crystallising oil. Diazotisation of this, followed by a Sandmeyer reaction (hydrobromic acid used at both stages), gave crude 3-bromo-4-methylacetophenone (8·4 g. from 10 g. acetamido-compound) as a low-melting solid. The oxime prepared from this had m. p. 94—95° (75—80° on admixture with the oxime described above), and the *semicarbazone* (small lustrous needles from pyridine) had m. p. 246—247° (230—235° when mixed with the foregoing semicarbazone) and was apparently slightly solvated after being dried in a vacuum (Found: C, 45·4; H, 4·6; N, 17·0. $C_{10}H_{12}ON_3Br$ requires C, 44·4; H, 4·5; N, 15·55%).

3-Chloro-2-nitro-4-methylacetophenone.—This *substance* (crude yield, 1 g.) was prepared from 2-nitro-3-amino-4-methylacetophenone (1 g.) using hydrochloric acid (25 c.c., 8N), sodium nitrite (8 c.c. of 5%), and cuprous chloride (from 1·6 g. of copper sulphate) in concentrated hydrochloric acid (2·5 c.c.). It formed almost colourless, fern-like blades, m. p. 128—129° (Found: C, 50·6; H, 3·5; Cl, 16·7. $C_9H_8O_3NCl$ requires C, 50·6; H, 3·8; Cl, 16·6%).

8-Chloro-4-hydroxy-7-methylcinnoline.—The foregoing nitro-ketone (0·6 g.), after reduction with acetic acid (5 c.c.), water (6 c.c.), and iron powder (1 g.), gave 0·45 g. of crude 3-chloro-2-amino-4-methyl-

acetophenone, m. p. 52—53°. This was dissolved in hydrochloric acid (10 c.c. of 2N and 3 c.c. of 12N) and diazotised (6 c.c. of 2% sodium nitrite), giving *8-chloro-4-hydroxy-7-methylcinnoline* (0·35 g.) as long, colourless, hair-like needles, m. p. 209—210° (Found: C, 55·1; H, 3·75; N, 14·2; Cl, 18·95. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·65; N, 14·4; Cl, 18·2%).

p-Chloroacetophenone.—By using acetyl chloride, this ketone was obtained in 80—90% yield by Straus and Ackerman (*Ber.*, 1909, **42**, 1804) and in 81% yield by Mayer, Stark, and Schön (*loc. cit.*). With acetic anhydride, Noller and Adams (*J. Amer. Chem. Soc.*, 1924, **46**, 1889) obtained an inferior yield (68%), but the following modification gave a yield of 93%. Acetic anhydride (2 mols., 186 c.c.) was slowly added (*ca.* 1 hour) to a well-stirred suspension of aluminium chloride (4·4 mols., 588 g.) in chlorobenzene (300 c.c.) at room temperature. The highly exothermic reaction proceeded smoothly and final heating on the water-bath for 1 hour brought about complete solution. The reaction mixture was poured on ice containing hydrochloric acid, and the product extracted with ether. The ethereal solution was washed with hydrochloric acid, sodium hydroxide solution, and water, dried, and concentrated. Distillation of the final residue yielded excess chlorobenzene followed by *p*-chloroacetophenone, b. p. 124—126°/*ca.* 30 mm.

4-Chloro-3-nitroacetophenone.—*p*-Chloroacetophenone (120 g.) was dissolved with vigorous stirring in concentrated sulphuric acid (278 c.c.) at − 12° to − 10° and treated with a mixture of nitric acid (*d* 1·5) and concentrated sulphuric acid (120 c.c., 1 : 2 v/v). Stirring was continued for a further 2 hours during which the nitration product began to separate. The suspension was poured on ice, and the moist solid recrystallised from methyl alcohol, giving short colourless blades, m. p. 102—103° (lit., 104°) (average yield 63%).

4-Chloro-3-acetamidoacetophenone.—4-Chloro-3-nitroacetophenone was reduced in 50-g. batches, and the amine (38·8 g., m. p. 106—108°) heated with acetic anhydride (80 c.c.) on the steam-bath for ½ hour; pure *4-chloro-3-acetamidoacetophenone* separated on cooling, and a further crop was obtained by basification of the filtrate with ammonia (average yield, 72% based on nitro-compound). The compound formed large, colourless tetrahedra, m. p. 118·5—119·5° (Found: C, 56·95; H, 4·75. $C_{10}H_{10}O_2NCl$ requires C, 56·7; H, 4·8%).

4-Chloro-2-nitro-5-aminoacetophenone.—4-Chloro-3-acetamidoacetophenone (20 g.) was added to nitric acid (110 c.c., *d* 1·5) at − 10° to − 5° during ½ hour. Stirring was continued for a further ½ hour, after which the solution was poured on ice (600 g.). Recrystallisation of the solid product from 3 batches (58 g.) yielded long, soft, white needles (16·6 g.) of *4-chloro-2-nitro-5-acetamidoacetophenone*, m. p. 142—143°, which turned red on exposure to light (Found: N, 11·4; Cl, 13·6. $C_{10}H_9O_4N_2Cl$ requires N, 10·9; Cl, 13·8%). *4-Chloro-2-nitro-5-aminoacetophenone* (76%) formed brittle purple-red needles, m. p. 169—170° (Found: C, 45·15; H, 3·55. $C_8H_7O_3N_2Cl$ requires C, 44·75; H, 3·3%).

Deamination of the nitro-amine was effected by treatment of its alcoholic suspension (0·5 g. in 7·5 c.c.) with concentrated sulphuric acid (0·5 c.c.) and amyl nitrite (2·5 c.c.) at 10°. The solution was warmed to the b. p., boiled for 5 minutes, and then largely diluted with water. The neutral product, isolated by ether extraction, was crystallised from ligroin, yielding needles of 4-chloro-2-nitroacetophenone, m. p. 53—54° alone and when mixed with an authentic specimen (prepared from 4-chloro-2-nitrobenzoic acid; following paper); admixture with 4-chloro-3-nitroacetophenone (m. p. 102—103°) depressed the m. p. to 44—46°.

4-Chloro-2-nitro-3-acetamidoacetophenone.—On the small scale, this substance was obtained by spontaneous evaporation of the alcoholic mother-liquor of the 5-acetamido-compound, followed by manual separation of the residual red and colourless crystals and recrystallisation of the latter. The *substance* formed colourless needles, m. p. 174—175° (Found: N, 11·25. $C_{10}H_9O_4N_2Cl$ requires N, 10·9%).

4-Chloro-2-nitro-3-aminoacetophenone.—This *amine*, obtained from the foregoing compound (yield, 80%), crystallised in large, golden, brittle plates, m. p. 94—95° (Found: C, 44·75; H, 3·3; N, 13·5. $C_8H_7O_3N_2Cl$ requires C, 44·75; H, 3·3; N, 13·05%). It was more conveniently prepared from the crude mixture of acetamido-compounds (after removal of the bulk of the 5-acetamido-derivative), as it is appreciably less soluble than 4-chloro-2-nitro-5-aminoacetophenone in alcohol. Reduction of the substance (0·2 g.) in acetic acid (5 c.c.) with iron powder (0·6 g.) and water (5 c.c.) gave the diamine, m. p. 87—89°; this (0·1 g.) was refluxed with phenanthraquinone (0·12 g.) in alcohol (20 c.c.) and yielded a phenazine, m. p. 287—288° alone and when mixed with the sample prepared (following paper) from 4-chloro-3-nitro-2-aminoacetophenone.

2 : 3 : 4-Trichloroacetophenone.—The diazonium solution prepared from 4-chloro-2-nitro-3-aminoacetophenone (2 g.), concentrated hydrochloric acid (40 c.c.), and sodium nitrite (5%, 16 c.c.) was added to cuprous chloride (from 3·2 g. of copper sulphate) in concentrated hydrochloric acid (12 c.c.). *2 : 3 : 4-Trichloroacetophenone* (crude yield, 1·5 g.) crystallised in long, colourless needles, m. p. 65·5—66° (Found: C, 42·9; H, 2·7; Cl, 47·4. $C_8H_5OCl_3$ requires C, 42·95; H, 2·2; Cl, 47·65%).

3 : 4-Dichloro-2-nitroacetophenone.—The suspension obtained by adding water (3·5 c.c.) to a solution of the above amine (2 g.) in sulphuric acid (18N, 26 c.c.) was treated with solid sodium nitrite (0·72 g.), and the resultant clear solution added to cuprous chloride (3·2 g. of copper sulphate) in concentrated hydrochloric acid (5 c.c.). Crude *3 : 4-dichloro-2-nitroacetophenone* (1·6 g., m. p. 170—190°) formed small, orange-pink needles, m. p. 195—196°, after recrystallisation (Found: C, 41·55; H, 2·35; N, 6·0. $C_8H_5O_3NCl_2$ requires C, 41·0; H, 2·1; N, 6·0%).

7 : 8-Dichloro-4-hydroxycinnoline and Derivatives.—The above nitro-compound (0·9 g.) in acetic acid (12 c.c.) was reduced with iron powder (2 g.) and water (6 c.c.), and the resultant crude amine (0·8 g., m. p. 78—79°) suspended in a mixture of concentrated (5 c.c.) and 2N-hydrochloric acid (15 c.c.). Solid sodium nitrite (0·4 g.) was added, and the solution filtered from a little insoluble matter. The *7 : 8-dichloro-4-hydroxycinnoline* which separated (0·5 g.) was virtually pure; the pure substance formed almost colourless needles, m. p. 253—254° (Found: C, 45·1; H, 2·2; N, 13·2; Cl, 33·1. $C_8H_4ON_2Cl_2$ requires C, 44·7; H, 1·85; N, 13·0; Cl, 33·0%). *4 : 7 : 8-Trichlorocinnoline* was prepared by heating the hydroxy-compound (0·4 g.) with phosphorus pentachloride (0·7 g.) and phosphorus oxychloride (1 c.c.) on the steam-bath for 1 hour; the mixture was poured on ice and a slight excess of aqueous

sodium hydroxide added. The chloro-compound, isolated by ether extraction, had m. p. 221—222° (yield, 0·3 g.). The substance could also be isolated from the reaction mixture by removal of excess phosphorus oxychloride (reduced pressure) and extraction of the residual solid with boiling ligroin, from which it separated in soft needles with a slight greenish tinge (Found: C, 41·1; H, 1·5; N, 12·65; Cl, 45·5. $C_8H_3N_2Cl_3$ requires C, 41·1; H, 1·3; N, 12·0; Cl, 45·6%). The trichlorocinnoline (0·3 g.) was heated with solid potassium hydroxide (0·1 g.) dissolved in phenol (1 g.) for 1 hour at 95°; addition of excess of aqueous sodium hydroxide followed by extraction with ether gave 7 : 8-*dichloro*-4-*phenoxycinnoline* (0·24 g.), m. p. 213—214°, sparingly soluble in ether and alcohol, and unchanged by crystallisation from ethyl acetate, from which it formed small colourless blades (Found: C, 57·6; H, 2·75; Cl, 24·6. $C_{14}H_8ON_2Cl_2$ requires C, 57·7; H, 2·8; Cl, 24·4%).

4 : 5-*Dichloro*-2-*nitroacetophenone*.—(*a*) The suspension obtained by cooling a hot solution of 4-chloro-2-nitro-5-aminoacetophenone (1 g.) in concentrated hydrochloric acid (29 c.c.) and water (7 c.c.) was diazotised and added to cuprous chloride as in the preparation of 2 : 3 : 4-trichloroacetophenone. 4 : 5-Dichloro-2-nitroacetophenone crystallised in pale brown needles, m. p. 100—102° alone and when mixed with material prepared by method (*b*).

(*b*) From 3 : 4-dichloroacetophenone. This ketone was obtained by Roberts and Turner (*loc. cit.*) in 40% yield, and the yield of nitration product is not recorded. The following conditions gave 3 : 4-dichloroacetophenone in 75% yield (based on acetyl chloride), and 55—60% yields of 4 : 5-dichloro-2-nitroacetophenone. Acetyl chloride (108 c.c.) was added during *ca.* 1 hour to a well-stirred suspension of aluminium chloride (443 g.) in *o*-dichlorobenzene (300 c.c.). After the initial reaction had moderated, the mixture was heated (stirring throughout) on the steam-bath for 2 hours, after which it was poured on ice and hydrochloric acid, and the ketone and excess of dichlorobenzene collected with ether. Distillation gave recovery of dichlorobenzene and then yielded 211 g. of ketone, b. p. 130—132°/13 mm., m. p. 75·5—76° from benzene–ligroin (b. p. 40—60°) (lit., 76°). The ketone (40 g.) was added during 10 minutes to nitric acid (200 c.c., *d* 1·5) at 35—38°. After a further 15 minutes within the same temperature limits, the solution was poured on ice (1 kg.) and the nitro-ketone filtered off, digested with warm aqueous sodium carbonate, and recrystallised; yield, 140 g. from 200 g.; m. p. 100—102° (lit., 100—102°). Our experience with this nitration confirms the necessity for working within the temperature ranges stated.

6 : 7-*Dichloro*-4-*hydroxycinnoline*.—4 : 5-Dichloro-2-aminoacetophenone, m. p. 157—159° (lit., 154—156°), was obtained in 91% yield by reduction of 50-g. batches of the nitro-compound; the substance was prepared by Roberts and Turner (*loc. cit.*), but no details are recorded. A hot suspension of the amine (40 g.) in concentrated hydrochloric acid (500 c.c.) and water (200 c.c.) was cooled and diazotised with aqueous sodium nitrite (20%, 72 c.c.). 6 : 7-*Dichloro*-4-*hydroxycinnoline* (38 g., 91%) had m. p. 333—334°, and separated from acetic acid, in which it was sparingly soluble, in small, colourless needles (Found: C, 44·6; H, 2·1; N, 13·45. $C_8H_4ON_2Cl_2$ requires C, 44·7; H, 1·85; N, 13·0%).

6 : 7-*Dichloro*-4-*acetoxycinnoline* (with C. M. Atkinson).—Prepared by refluxing the hydroxy-compound (0·5 g.) with acetic anhydride (2·5 c.c.) for 1 hour, this *substance* formed irregular clusters of colourless needles, m. p. 148—149° (Found: N, 11·15; Cl, 27·5. $C_{10}H_6O_2N_2Cl_2$ requires N, 10·9; Cl, 27·6%).

4 : 6 : 7-*Trichlorocinnoline*.—This *compound* (yield, 85—90%) was prepared as for the 4 : 7 : 8-isomer from the hydroxycinnoline (24 g.), phosphorus pentachloride (42 g.), and phosphorus oxychloride (60 c.c.); the reaction was very rapid when the mixture was gently warmed on the water-bath, in notable contrast to the chlorination of nitro-4-hydroxycinnolines. The trichlorocinnoline, sparingly soluble in ether and ligroin, crystallised from the latter solvent in small pale yellow needles, m. p. 141·5—142·5° (Found: C, 41·5; H, 1·8; N, 12·65; Cl, 44·7. $C_8H_3N_2Cl_3$ requires C, 41·1; H, 1·3; N, 12·0; Cl, 45·6%); it is stable for a few days at least, but gradually undergoes hydrolysis in moist air; a sample which had been bottled for 3 months without special precautions had m. p. 317—319° alone and when mixed with the hydroxycinnoline.

6 : 7-*Dichloro*-4-*phenoxycinnoline*.—Prepared as for the 7 : 8-dichloro-isomer from the trichloro-compound (22·5 g.), potassium hydroxide (6 g.), and phenol (60 g.), this *cinnoline* (yield, 85%) crystallised in long, colourless needles, m. p. 162—163°, sparingly soluble in ether (Found: C, 57·6; H, 2·75; Cl, 24·7. $C_{14}H_8ON_2Cl_2$ requires C, 57·7; H, 2·8; Cl, 24·4%).

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Warrington Yorke Department of Chemotherapy,
Liverpool School of Tropical Medicine. [*Received, June 17th*, 1946.]

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54. *Cinnolines. Part X. The Preparation of 4-Chloro-2-aminoacetophenone and Related 4-Hydroxycinnolines.*

By C. M. Atkinson and J. C. E. Simpson.

A description is given of preparative routes to 4-*chloro*-2-*aminoacetophenone*, from which 7-*chloro*-4-*hydroxycinnoline* is prepared by diazotisation and ring closure.

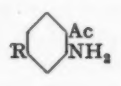
Similar treatment of 4-*chloro*-5- and -3-*nitro*-2-*aminoacetophenone* in sulphuric acid solution yields, respectively, 7-*chloro*-6- and -8-*nitro*-4-*hydroxycinnoline*. Diazotisation of the chloro-

nitro-amino-ketones in hydrochloric acid solution, however, produces, respectively, 6 : 7- and 7 : 8-dichloro-4-hydroxycinnoline.

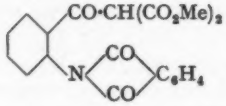
It is shown that the exchange of groups involved in the formation of the dichlorocinnolines occurs after diazotisation, but precedes the ring closure, and is thus an exchange reaction of the diazonium kations.

For various reasons we were interested in the preparation of cinnoline derivatives carrying a chlorine atom on C_7. The accessibility of such compounds clearly depended on the establishment of a relatively easy route to 4-*chloro*-2-*aminoacetophenone* (I; R = Cl). Several unsuccessful attempts to prepare this substance are mentioned by Roberts and Turner (*J.*, 1927, 1832), and it seemed unlikely that further investigation of the methods employed by them would prove successful.

In our own approach to the problem we were impressed by the statement of Gabriel and Löwenberg (*Ber.*, 1918, **51**, 1493) that methyl 2-phthalimidobenzoylmalonate (II) yields *o*-aminoacetophenone (I; R = H) on treatment with hydriodic acid. Phthaloylation of



(I.)



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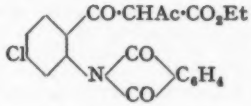


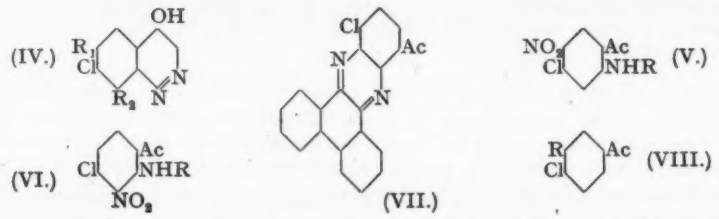
(III.)

4-chloroanthranilic acid by fusion of the dry components (a method which is apparently satisfactory with anthranilic acid; Gabriel and Löwenberg, *loc. cit.*) was unreliable on the large scale, and the use of α-chloronaphthalene as solvent, although it induced a very rapid reaction, also gave erratic results. In glacial acetic acid solution, however (cf. *Chem. Abstr.*, 1944, **38**, 1221), a slow but smooth reaction occurred, furnishing 4-*chloro*-2-*phthalimidobenzoic acid* in about 70% yield, and, after much experimenting, the amino-ketone (I; R = Cl) was obtained as the N-*acetyl* derivative in a yield of about 45% (based on the acid) by condensation of 4-chloro-2-phthalimidobenzoyl chloride with malonic ester, hydrolysis with hydrobromic acid, and acetylation. An attempt was made to substitute acetoacetic for malonic ester, but here the results were not encouraging; some *ethyl* 4-*chloro*-2-*phthalimidobenzoylacetoacetate* (III) was readily isolated, but hydrolysis gave 4-chloroanthranilic acid as the only isolable product under the conditions used, and the route was not further explored.

We also examined the possibility of preparing (I; R = Cl) from 4-chloro-2-nitrobenzoic acid. Grohmann (*Ber.*, 1891, **24**, 3808) prepared this acid on the small scale, apparently in high yield, by bomb-tube oxidation of 4-chloro-2-nitrotoluene with dilute nitric acid, but we were unable to find a satisfactory large-scale method of achieving this oxidation. Preparation of the acid *via* the nitrile was more successful; hydrolysis of the latter proceeded smoothly (cf. Heller, *Ber.*, 1916, **49**, 523), but we could not substantiate the yield claimed either by Heller (*loc. cit.*) or by Hunn (*J. Amer. Chem. Soc.*, 1923, **45**, 1024) for the preparation of the nitrile from 4-chloro-2-nitroaniline, and a modification (giving 50% yield) of Hunn's method was therefore used. Condensation of 4-chloro-2-nitrobenzoyl chloride with ethyl acetoacetate proceeded smoothly, and hydrolysis of the product, following the method of Kermack and Smith (*J.*, 1929, 814), gave 4-*chloro*-2-*nitroacetophenone* in 74% yield (based on the acid). Reduction of the nitro-ketone to (I; R = Cl) was almost quantitative.

For reasons already advanced (Schofield and Simpson, *J.*, 1945, 520), we did not anticipate that a high yield of 7-*chloro*-4-*hydroxycinnoline* (IV; $R_1 = R_2 = H$) would result from diazotisation of 4-chloro-2-aminoacetophenone. The yield actually obtained (about 30%) is, as expected, intermediate between the yields of products obtained from *o*-aminoacetophenone on the one hand (*ca.* 10%) and from 5-nitro-, 5-cyano-, and 5-halogeno-2-aminoacetophenones (*ca.* 70—90%) on the other. It was further to be expected from earlier results (Schofield and Simpson, *loc. cit.*) that introduction of a nitro-group into the 5- or 3-position of the chloroaminoacetophenone would substantially favour cinnoline formation, and this also proved to be the case. Nitration of 4-chloro-2-acetamidoacetophenone gave, as main product, 4-*chloro*-5-*nitro*-2-*acetamidoacetophenone* (V; R = Ac), together with a small amount of the 3-*nitro*-isomer (VI; R = Ac). Diazotisation and cyclisation, in sulphuric acid solution, of the corresponding *amines* (V and VI; R = H) furnished 7-*chloro*-6-*nitro*- (IV; $R_1 = NO_2$; $R_2 = H$) and 7-*chloro*-8-*nitro*-4-*hydroxycinnoline* (IV; $R_1 = H$; $R_2 = NO_2$) as sole isolable products. The orientation of (VI; R = H) was proved by reduction and conversion into the *phenazine* (VII); by elimination, therefore, the constitution (V; R = H) could be confidently assigned

to the isomeric nitroamine, but formal proof of this orientation is provided by the work described below.



From our experience with various examples of cinnoline synthesis it would seem that the ring closures are independent, qualitatively, of the nature of the mineral acid used at the diazotisation stage, although it is customary to use hydrochloric acid for this purpose except in the case of very weak amines. It is therefore of interest that, when the diazotisations of (V; R = H) and (VI; R = H) were performed in hydrochloric acid, the sole isolable products were, respectively, 6 : 7-dichloro-4-hydroxycinnoline (IV; R_1 = Cl; R_2 = H) [thus proving the structure of (V; R = H)] and the 7 : 8-isomeride (IV; R_1 = H; R_2 = Cl). An exchange of groups is clearly involved in these reactions, and it became of interest to ascertain the precise stage at which this exchange occurs. This point was settled by deamination. Diazotisation of (V; R = H) in hydrochloric acid, followed by immediate addition to hypophosphorous acid, gave a mixture from which 4-chloro-3-nitroacetophenone (VIII; R = NO_2) was isolated, thus proving that the normal diazonium kation is an intermediate stage in the formation of 6 : 7-dichloro-4-hydroxycinnoline. When, however, the deamination was preceded by gentle warming of the diazotised solution until the first sign of dichlorocinnoline formation was evident, the sole deamination product was 3 : 4-dichloroacetophenone (VIII; R = Cl). Similar treatment of (VI; R = H) also gave the same ketone (no attempt was made in this case to achieve deamination without interchange of groups). Now it has already been stated that the dichlorohydroxycinnolines are the only isolable products when the respective reactions are carried through to completion, and it therefore follows, from these results and from the formation of 3 : 4-dichloroacetophenone, that the group exchange is effected principally by the attack of chloride ion on the (normal) diazonium kation before cyclistion (although the possibility cannot be entirely excluded that simultaneous ring closure and group interchange might also contribute in some measure to the final result).

That atypical transformations may occur in monocyclic aromatic diazonium salts was shown many years ago by Meldola and his co-workers (*J.*, 1900, **77**, 1172; 1901, **79**, 1076; 1902, **81**, 988) in the case of certain dinitroanisidines, which, so far as we are aware, are the only examples on record in the benzene series, although reactions of this type are more prone to occur with naphthalene compounds (*e.g.*, Morgan, *J.*, 1902, **81**, 1376; also references below). We have encountered other instances (unpublished) of reactions of substituted aminoacetophenones which appear to be essentially of the same type, and the formation of 2 : 3 : 4-trichloroacetophenone from 4-chloro-2-nitro-3-aminoacetophenone (Keneford and Simpson, preceding paper) is a further example of the same process, but until fuller knowledge of the governing factors is available it is not possible to define the scope of the reaction. The point we would stress, however, is that, in extension of Meldola's results (*locc. cit.*), our observations show that a substituted diazonium kation may become involved in an exchange of groups before removal of the diazonium residue, and that slight variations in experimental conditions, such as gentle warming, may suffice to determine whether or not such an interchange occurs. It is therefore possible to postulate, on grounds of analogy, a similar susceptibility for the diazonium kation derived from 1-nitro-2-aminonaphthalene, and thus to explain some apparently discordant results in the literature of this compound, in particular the production from it (after diazotisation in each case with hydrochloric acid and sodium nitrite) of 1-chloro-2-fluoro-, 1 : 2-dichloro-, and 2-chloro-1-bromo-naphthalene, according to conditions (Clemo, Cockburn, and Spence, *J.*, 1931, 1265; Willstaedt and Scheiber, *Ber.*, 1934, **67**, 466; Schiemann and Ley, *ibid.*, 1936, **69**, 960).

Experimental.

(Melting points are uncorrected.)

4-Chloro-2-phthalimidobenzoic Acid.—4-Chloroanthranilic acid (100 g.) and phthalic anhydride (100 g.) were ground together in a mortar, and the mixture refluxed in acetic acid (500 c.c.) for 7 hours. Small colourless prisms separated from the boiling solution, which was allowed to cool overnight,

whereupon the *phthalimido-acid* was filtered off (122 g.; 69%), m. p. 269—270° (Found: C, 59·65; H, 2·55. $C_{15}H_8O_4NCl$ requires C, 59·7; H, 2·65%). If the cooling of the reaction mixture were too prolonged, low-melting material sometimes separated along with the product, which in such cases could be purified by digestion with alcohol.

4-Chloro-2-acetamidoacetophenone.—Three successive experiments (carried out by Mr. J. R. Keneford) gave yields of 25·6, 27·5, and 28 g. of acetamido-ketone (average, 45·8%). In two of our own earlier experiments the conditions were as described below except that the last traces of phosphorus oxychloride were removed by repeated evaporation with benzene under reduced pressure. This treatment is apparently disadvantageous, as the yields of acetamido-ketone were 21 and 24 g. The above acid (84 g.) and phosphorus pentachloride (64 g.) were refluxed in dry benzene (600 c.c.) for one hour. Solvent and phosphorus oxychloride were removed under reduced pressure and the resultant solid was immediately redissolved in dry, slightly warm benzene (900 c.c.). This clear solution was added dropwise during ½ hour to a well-stirred suspension of ethyl sodiomalonate prepared the previous day by addition, during 20 minutes, of ethyl malonate (108 c.c.) in benzene (300 c.c.) to a rapidly-stirred suspension of powdered sodium (12·8 g.) in benzene (500 c.c.), the suspension of ethyl sodiomalonate being then refluxed for 4 hours (cf. Wilds and Beck, *J. Amer. Chem. Soc.*, 1944, **66**, 1688). After the addition of the acid chloride, stirring was continued for 5 hours, and the turbid yellow reaction mixture allowed to stand overnight and then decomposed with 3N-hydrochloric acid (500 c.c.). The aqueous layer was extracted with ether and the extract combined with the original benzene layer, washed, dried, and concentrated. The oil so obtained was refluxed for 8 hours with hydrobromic acid (*d* 1·5, 600 c.c.), after which the mixture was cooled, basified with ammonia, and extracted with ether. Crude 4-chloro-2-aminoacetophenone was obtained by evaporation of this extract, after washing and drying, as a sweet-smelling, readily crystallising oil; acetylation with acetic anhydride (2 parts) gave fine white needles of pure *4-chloro-2-acetamidoacetophenone*, m. p. 148—150°, directly from the reaction mixture (Found: C, 56·55; H, 4·8. $C_{10}H_{10}O_2NCl$ requires C, 56·7; H, 4·7%).

4-Chloro-2-aminoacetophenone.—The above acetoamido-compound (1·5 g.) was refluxed for 15 minutes with hydrochloric acid (24 c.c., 5N); the mixture was then cooled and basified with ammonia. The *amino-ketone* separated from aqueous alcohol in small white needles, m. p. 91—93° (1·15 g.) (Found: C, 56·2; H, 4·65. C_8H_8ONCl requires C, 56·6; H, 4·7%).

Ethyl 4-Chloro-2-phthalimidobenzoylacetoacetate.—A mixture of ethyl acetoacetate (3 g.) and sodium ethoxide (1 g. of sodium; 18 c.c. of alcohol) was cooled to 5° and treated with a solution of 4-chloro-2-phthalimidobenzoyl chloride (prepared from 6 g. of the acid as above) in dry benzene (50 c.c.). The yellow solution was kept overnight at room temperature, and then decomposed with hydrochloric acid and extracted with ether. Concentration of the washed and dried extract gave the *ester* (3·6 g.), which crystallised from alcohol in white leaflets, m. p. 104° (Found: C, 60·6; H, 4·5; N, 4·0. $C_{21}H_{16}O_6NCl$ requires C, 60·9; H, 3·9; N, 3·4%).

For hydrolysis, the above compound (1·5 g.) was refluxed for ¾ hour with hydriodic acid (*d* 1·7; 4·5 c.c.), after which the solution was concentrated under reduced pressure on the steam-bath, and the residue basified with sodium carbonate and extracted with ether. The extract yielded a dark, crystallising oil (0·14 g.) which in no way resembled 4-chloro-2-aminoacetophenone; acidification of the alkaline mother-liquor yielded only 4-chloroanthranilic acid, m. p. and mixed m. p. 237° (decomp.) (Found: C, 48·85; H, 3·3; Cl, 20·5. Calc. for $C_7H_6O_2NCl$: C, 49·0; H, 3·5; Cl, 20·7%). In a second experiment, 1·5 g. were treated with a mixture of alcohol (7·5 g.) and sulphuric acid (1 g.) according to the method of Kermack and Smith (*loc. cit.*); the product was a pale yellow oil (1·2 g.) which could not be crystallised.

4-Chloro-2-nitrobenzonitrile.—(*a*) (Method of Hunn, *loc. cit.*). A solution of 4-chloro-2-nitroaniline (17·25 g.) in concentrated sulphuric acid (15 c.c.) was poured into water (170 c.c.) with vigorous stirring, and the finely divided suspension diazotised at 10° with sodium nitrite (7 g.) in water (70 c.c.), added during 2 hours. After a further hour's stirring, the filtered solution was added gradually to a solution of copper sulphate (43 g.) and sodium cyanide (34·5 g.) in water (215 c.c.). After 2 hours at room temperature, the mixture was heated at 70° for ½ hour, cooled, and filtered. The partly dried solid was steam-distilled from a flask immersed in an oil-bath at 180°, and the steam-volatile material isolated by ether extraction. Almost pure nitrile (m. p. 94—96°) was thus obtained [yield, 5 g., 27%; Hunn (*loc. cit.*) claims 75%].

(*b*) 4-Chloro-2-nitroaniline (34·5 g.) was diazotised exactly as described above, the solution filtered, treated with saturated aqueous sodium acetate until neutral to Congo-red, and added at 70° to a solution of copper sulphate (56 g.) and alkali cyanide ("double salt", 60 g.) in water (280 c.c.). The product was collected with ether, and the extract, after being washed with sodium hydroxide solution and water, was dried and evaporated. The yield of crude nitrile (31·5 g.) was not significantly altered when the reaction temperature was *ca.* 20°, or when the addition of sodium acetate was omitted (reaction temperature either 70° or 20°). Percolation through alumina (Merck), elution with benzene, and digestion of the solute with a little ether gave the pure nitrile (77·2 g. from 123 g.), m. p. 100—101°.

4-Chloro-2-nitrobenzoic Acid.—(*a*) Potassium permanganate (20 g.) was added during 24 hours to a refluxing suspension of 4-chloro-2-nitrotoluene (10 g.) in water (250 c.c.), the condenser being cleared of steam-volatile material from time to time. Filtration and acidification gave 4-chloro-2-nitrobenzoic acid (2·6 g.), m. p. 140—141° alone and when mixed with an authentic sample prepared from 2-nitro-4-aminobenzoic acid; unoxidised chloronitrotoluene (4·6 g.) was recovered from the manganese dioxide precipitate by ether extraction. This result could not be reproduced on a larger scale (with slight variations). The chloronitrotoluene was not attacked by a mixture (1 : 1) of concentrated nitric acid and water under reflux; bromination at 160—170° followed by oxidation (cf. Norris and Bearse, *J. Amer. Chem. Soc.*, 1940, **62**, 953) was ineffective, as the bromination was not confined to the side chain; and oxidation with permanganate in aqueous pyridine was unsuccessful.

(*b*) 4-Chloro-2-nitrobenzonitrile (10 g., m. p. 97—98°) was heated on the steam-bath with sulphuric acid (80 c.c. of 80%, v/v) for 1½ hours; the clear solution was then diluted with water (48 c.c.) and gently refluxed for 1½ hours. The oily suspension was cooled, water (130 c.c.) added, and the crystalline

acid filtered off and reprecipitated from sodium carbonate solution (charcoal); yield 8·8 g., m. p. 141—143°. In one or two experiments the yields were extremely poor, apparently owing to the fact that in these cases the concentration of the acid used was slightly greater than 80% (v/v).

4-Chloro-2-nitroacetophenone.—4-Chloro-2-nitrobenzoyl chloride was prepared (cf. Cohen and Armes, *J.*, 1906, **89**, 458) from 4-chloro-2-nitrobenzoic acid (24 g.) and phosphorus pentachloride (27 g., 1·1 mols.), the vigorous spontaneous reaction being completed by heating for 1½ hours on a steam-bath. Phosphorus oxychloride was removed under reduced pressure, and the resultant oil dissolved in dry benzene (50 c.c.). A solution of sodium ethoxide (from sodium, 6·15 g., and absolute alcohol, 100 c.c.), was divided into two equal parts. To one was added with stirring ethyl acetoacetate (17·85 g.), and this solution, cooled to 0°, was treated simultaneously with the acid chloride solution and the remainder of the sodium ethoxide by addition, at approximately equal rates (¾ hour), through two dropping funnels. After a further 3 hours (temperature below 5°; mechanical stirring throughout) the mixture was kept overnight at room temperature, and then decomposed with dilute hydrochloric acid and extracted with ether. The extract was washed with sodium bicarbonate solution and water, dried, and evaporated, yielding a red mobile oil (35 g.). This (17 g.) was hydrolysed with 10% (w/w) alcoholic sulphuric acid (255 g.) (manipulation according to Kermack and Smith, *loc. cit.*) and yielded *4-chloro-2-nitroacetophenone* as clusters of soft, white needles (8·8 g., m. p. 55—56°) from ether–ligroin (b. p. 60—80°) (Found: C, 48·25; H, 3·05. $C_8H_6O_3NCl$ requires C, 48·1; H, 3·0%). Reduction of the nitroketone (6·5 g.) with acetic acid (50 c.c.), iron powder (13 g.), and water (12 c.c.) in the known manner (*J.*, 1945, 646) gave 4-chloro-2-aminoacetophenone (4·7 g., 85%), m. p. [from ligroin (b. p. 60—80°)] 91—93° alone and when mixed with the material described earlier.

4-Chloro-5-nitro-2-aminoacetophenone.—4-Chloro-2-acetamidoacetophenone (10 g.) was added during 35 minutes to a mechanically stirred mixture of nitric acid (*d* 1·48) and concentrated sulphuric acid (5 : 2 v/v; 60 c.c.) at a temperature below − 10°. After a further 20 minutes the solution was poured on ice, and the product filtered off and washed. *4-Chloro-5-nitro-2-acetamidoacetophenone* separated from alcohol in slender yellow blades (9·4 g., 77%), m. p. 166—168° (Found: C, 46·5; H, 3·5. $C_{10}H_9O_4N_2Cl$ requires C, 46·8; H, 3·5%). This substance was hydrolysed by refluxing it (4 g.) with a mixture of alcohol (40 c.c.), water (40 c.c.), and concentrated hydrochloric acid (40 c.c.). More alcohol was added to dissolve the solid which rapidly separated, and after 10 minutes the solution was concentrated and basified; *4-chloro-5-nitro-2-aminoacetophenone* (3·2 g.) separated in fine yellow needles, m. p. 176—177°, unchanged by crystallisation from alcohol (Found: C, 45·2; H, 3·2; N, 13·05; Cl, 16·45. $C_8H_7O_3N_2Cl$ requires C, 44·8; H, 3·3; N, 13·05; Cl, 16·5%).

4-Chloro-3-nitro-2-aminoacetophenone.—The aqueous mother-liquor from the above nitration was basified with sodium carbonate and extracted with ether, and the extract was washed and dried. Concentration to a small volume yielded almost colourless needles of *4-chloro-3-nitro-2-acetamidoacetophenone* (0·5 g.), m. p. 142—143° (depressed by admixture with 4-chloro-2-acetamidoacetophenone and with the 5-nitro-isomer described above) (Found: C, 47·15; H, 3·45. $C_{10}H_9O_4N_2Cl$ requires C, 46·8; H, 3·5%). Hydrolysis of the compound (0·3 g.), carried out as for the 5-nitro-isomer, yielded the free *amine* as yellow plates (0·23 g., m. p. 148—150°), unchanged by crystallisation from alcohol (Found: C, 44·5; H, 3·2; Cl, 16·7. $C_8H_7O_3N_2Cl$ requires C, 44·8; H, 3·3; Cl, 16·5%). When the amine (0·2 g.) was reduced with iron (0·5 g.) and acetic acid (5 c.c.) and worked up as described above, the corresponding diamine (0·19 g.) was obtained as a readily crystallising oil. This was refluxed with phenanthraquinone (0·22 g.) in alcohol (30 c.c.) for 7 hours (condensation was incomplete after ½ hour). The fine brown needles of the *phenazine* (VII) were filtered off hot; m. p. 287° after crystallisation from acetic acid (Found: C, 74·2; H, 3·65. $C_{22}H_{13}ON_2Cl$ requires C, 74·0; H, 3·7%).

7-Chloro-4-hydroxycinnoline.—4-Chloro-2-aminoacetophenone (3 g.) was suspended in hydrochloric acid (6N, 60 c.c.), cooled to 5°, diazotised with sodium nitrite (1·3 g.) in water (10 c.c.), and the solution so formed heated on a steam-bath until the coupling reaction was negative. The resultant crude solid was dissolved in warm dilute aqueous sodium hydroxide, reprecipitated with hydrochloric acid, and washed with ether, which removed a fragrant-smelling oil, presumably 4-chloro-2-hydroxyacetophenone. Pure *7-chloro-4-hydroxycinnoline* (1·07 g., m. p. 276—277°) separated from alcohol in colourless needles (Found: C, 52·9; H, 2·75; N, 15·25. $C_8H_5ON_2Cl$ requires C, 53·2; H, 2·8; N, 15·5%).

7-Chloro-6-nitro-4-hydroxycinnoline.—A solution of 4-chloro-5-nitro-2-aminoacetophenone (0·5 g.) in glacial acetic acid (7·5 c.c.), concentrated sulphuric acid (2 c.c.), and water (0·5 c.c.) was diazotised at 5° with solid sodium nitrite (0·18 g.). The slightly turbid solution was heated at 80—85° for 1 hour (coupling reaction then negative) and was then diluted with water (10 c.c.). The product which separated was dissolved in 0·25N-aqueous sodium hydroxide, precipitated by dilute acid (yield, 0·3 g.), and recrystallised from acetic acid, from which *7-chloro-6-nitro-4-hydroxycinnoline* separated in stout bronze needles, m. p. 252—254° (decomp.) (Found: C, 42·9; H, 2·0; N, 18·4; Cl, 15·4. $C_8H_4O_3N_2Cl$ requires C, 42·6; H, 1·8; N, 18·6; Cl, 15·7%), moderately soluble in aqueous sodium bicarbonate, easily soluble in dilute sodium hydroxide, but more difficultly soluble in 2N-sodium hydroxide owing to the tendency for the sodium salt to separate (minute yellow needles).

7-Chloro-8-nitro-4-hydroxycinnoline.—Diazotisation of 4-chloro-3-nitro-2-aminoacetophenone (0·5 g.) and purification of the crude product as described above gave material (0·3 g.), m. p. 254—255° (decomp.). Recrystallisation from alcohol furnished *7-chloro-8-nitro-4-hydroxycinnoline* as jagged yellow needles, m. p. 262—264° (decomp.) (Found: C, 42·8; H, 2·1; N, 18·1; Cl, 16·0. $C_8H_4O_3N_2Cl$ requires C, 42·6; H, 1·8; N, 18·6; Cl, 15·7%).

6 : 7-Dichloro-4-hydroxycinnoline.—A well-stirred suspension of 4-chloro-5-nitro-2-aminoacetophenone (5 g.) in hydrochloric acid (6N, 60 c.c.) was diazotised at 5—10° with 10% sodium nitrite solution. After being stirred for several hours at room temperature, the almost clear solution was set aside overnight and then heated on the steam-bath as above. The product, which separated from the hot solution, was purified by solution in dilute aqueous alkali, reprecipitation, and crystallisation from boiling acetic acid, yielding 6 : 7-dichloro-4-hydroxycinnoline (3 g.) as soft fawn leaflets, m. p. 333° (decomp.) alone and when mixed with a sample prepared as in the previous paper (Found: C, 44·8; H 2·4; N, 13·35; Cl, 32·5. Calc. for $C_8H_4ON_2Cl_2$: C, 44·7; H, 1·85; N, 13·0; Cl, 33·0%). For

further identification, the substance was converted into the 4-acetoxy-compound, m. p. 148—149°, and the 4-chloro-compound, m. p. 141·5—143°, and the latter was characterised as the 4-phenoxy-derivative, m. p. 162—163° (Found: C, 57·3; H, 2·7. Calc. for $C_{14}H_8ON_2Cl_2$: C, 57·7; H, 2·8%). These reactions were carried out as described in the previous paper, and each derivative was identified by mixed m. p. with an authentic sample.

7 : 8-*Dichloro-4-hydroxycinnoline.*—A suspension of 4-chloro-3-nitro-2-aminoacetophenone (0·67 g.) in hydrochloric acid (6N, 30 c.c.) was cooled in ice and diazotised with solid sodium nitrite (the reaction was slow and the suspension was finally left overnight at room temperature; an excess of nitrite had therefore to be used to compensate for loss of oxides of nitrogen). Cyclisation of the diazonium salt and purification of the crude product were carried out as described for the foregoing isomer, and yielded 0·5 g. of nearly pure 7 : 8-dichloro-4-hydroxycinnoline, which after one crystallisation from alcohol formed almost colourless needles, m. p. 253—254° alone and mixed with a specimen prepared from 3 : 4-dichloro-2-aminoacetophenone (previous paper). The derived 4 : 7 : 8-trichlorocinnoline, m. p. 217—218°, and 7 : 8-dichloro-4-phenoxycinnoline, m. p. 214·5°, gave no depressions in m. p. when mixed with authentic samples.

Deamination Experiments with 4-Chloro-5- and -3-nitro-2-aminoacetophenones.—(*a*) The 5-nitro-compound (0·5 g.) was diazotised in hydrochloric acid (6 c.c., 6N) as above, and the clear solution (after recovery of 0·2 g. of unreacted amine) was added at 0° during 10 minutes to 30% hypophosphorous acid (10 c.c.). After 4 hours at 0° the solid, which had gradually separated, was filtered off, washed, and dried; it had m. p. 84—87°, depressed to 62—66° on admixture with 3 : 4-dichloroacetophenone (m. p. 75—77°). After two crystallisations from alcohol the m. p. was 98—99° alone and when mixed with 4-chloro-3-nitroacetophenone (m. p. 99—101°).

(*b*) Diazotisation of the foregoing amine (3 g.) as above gave a 50% recovery of unchanged material. The filtrate was heated on the steam-bath until a slight turbidity occurred; it was then cooled rapidly in ice and added during a few minutes to 30% hypophosphorous acid (60 c.c.) with mechanical stirring. After standing for several days at 0°, the solid product was digested with warm dilute sodium hydroxide solution, filtered off, washed, and dried. The material (0·66 g., m. p. 71—73°) could not be further purified by crystallisation, but sublimed almost completely at 50—60°/0·05 mm., yielding pure 3 : 4-dichloroacetophenone, m. p. and mixed m. p. 76—77°.

(*c*) Diazotisation of 4-chloro-3-nitro-2-aminoacetophenone (1 g.) in hydrochloric acid (6N, 44 c.c.) at room temperature gave a 50% recovery of unchanged amine. Treatment of the filtrate as in (*b*) gave crude 3 : 4-dichloroacetophenone (0·25 g., m. p. 71—73°), which sublimed almost completely at 50—70°/0·05 mm. (m. p. and mixed m. p. 75—77°). The alkali-soluble material was identified as 7 : 8-dichloro-4-hydroxycinnoline by m. p. and mixed m. p.

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WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.
DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM.

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55. *Cinnolines. Part XI.* 8-*Nitro*-4-*hydroxycinnoline.*

By J. C. E. SIMPSON.

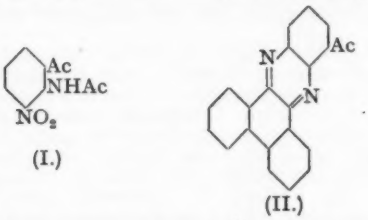
The substance previously formulated as 5-nitro-4-hydroxycinnoline (Schofield and Simpson, *J.*, 1945, 512) is shown to be the 8-nitro-isomer by an unambiguous synthesis from 3-nitro-2-aminoacetophenone.

IT was recently shown (*loc. cit.*) that the nitration of 4-hydroxycinnoline produces three mononitro-derivatives. Of these, one, m. p. 331°, was identified as the 6-nitro-compound, a second, m. p. 185°, was regarded as the 5-isomer on account of its failure to react with acetic anhydride, this being attributed to steric causes, and the third isomer, m. p. 277°, was accordingly formulated as 7 (or 8)-nitro-4-hydroxycinnoline.

The nitration of *o*-acetamidoacetophenone was previously stated (*J.*, 1945, 646) to give only 5-nitro-2-acetamidoacetophenone, but under somewhat different conditions 3-*nitro*-2-*acetamido-acetophenone* (I) is also formed, together with a small amount of an unidentified *substance*, $C_{10}H_9O_2N_3$, which appears to be neither a primary amine nor an acetamido-compound. Hydrolysis of (I) gave 3-nitro-2-aminoacetophenone, originally obtained in small amount by Bamberger (*Ber.*, 1915, **48**, 537) from 2-nitroaminoacetophenone, but not oriented by him; its constitution has now been proved by conversion into the phenazine (II), previously obtained (*J.*, 1945, 646) from 2-nitro-3-aminoacetophenone.

Diazotisation and cyclisation of 3-nitro-2-aminoacetophenone gave a product identical with the nitro-hydroxycinnoline, m. p. 185°, referred to above; this substance is, therefore, the 8-, and not the 5-, isomer. Its failure to react with acetic anhydride is therefore to be

ascribed to chelation, and it must accordingly be represented by (III) rather than by (IV). The substance has been examined spectrographically by Professor R. A. Morton, and the results,



(I.) (II.) (III.) (IV.)

which will be published later, are in conformity with the structure advocated, as also is the comparatively low melting point of the compound.

Experimental.

Melting points are uncorrected.

Nitration of o-*Acetamidoacetophenone.*—The ketone (50 g.) was added in small portions to a mixture of nitric acid (250 c.c., *d* 1·48) and concentrated sulphuric acid (50 c.c.) with stirring; the addition was made as rapidly as possible (½—¾ hour) consistent with a reaction temperature of 0° to − 8°. The mixture was then added to crushed ice (600 g.) and water (200 c.c.), and the crude nitration product filtered off and washed (filtrate A). The solid from three runs was digested with boiling alcohol (1 l.) and filtered off cold, yielding a product, m. p. *ca.* 130—145°. Crystallisation from the minimum volume of boiling alcohol (*ca.* 3·5 l.) gave a mixture of needles and stout yellow prisms, the former predominating. After rough manual separation, the needles were recrystallised from alcohol and gave pure 5-nitro-2-acetamidoacetophenone, m. p. 154—155°; the prisms, recrystallised from benzene, yielded 3-*nitro*-2-*acetamidoacetophenone*, which formed very pale yellow prisms, m. p. 152—153° (*cf.* 125—130° when mixed with the 5-nitro-isomer) (Found: C, 54·0; H, 4·65. $C_{10}H_{10}O_4N_2$ requires C, 54·0; H, 4·55%). A further crop of the 3-nitro-isomer was obtained from the first two alcoholic filtrates.

All alcoholic mother-liquors then remaining, including those from the nitration of two 25-g. batches under the earlier conditions (*J.*, 1945, 646), were bulked, solvent removed, and the residue repeatedly crystallised from benzene, yielding pure 5-nitro-2-aminoacetophenone (3 g.; m. p. and mixed m. p.). More of this amine was obtained from the total benzene filtrates by removal of solvent, acid hydrolysis, and crystallisation of the mixed amines from benzene.

The filtrates (A) were made just alkaline (ice and ammonia) and thoroughly extracted with ether. The extract was washed with a little water, dried, and evaporated, and the residue crystallised from methanol and finally from ethanol, yielding a sparingly soluble *base*, m. p. 201—202° (slight shrinking at 190°) (Found: C, 59·0, 59·2; H, 4·7, 4·6; N, 20·3, 20·5. $C_{10}H_9O_3N_3$ requires C, 59·1; H, 4·4; N, 20·7%). The compound formed deep yellow, brittle needles, insoluble in cold aqueous sodium bicarbonate or hydroxide, and soluble in cold 2N-hydrochloric acid. It was not attacked by 4N-hydrochloric acid (1½ hours on the steam-bath), and did not visibly couple with alkaline β-naphthol after diazotisation.

The methanol filtrate from the foregoing compound gave a small crop of 3-nitro-2-acetamidoacetophenone; evidence of traces of other compounds was obtained, but these were not investigated. After hydrolysis of the 5-nitro-compound, the final yields from 200 g. of *o*-acetamidoacetophenone were 133 g. of 5-nitro-2-aminoacetophenone, 21 g. of 3-nitro-2-acetamidoacetophenone, and 4·3 g. of the substance, m. p. 201—202°. 3-Nitro-2-acetamidoacetophenone is more soluble than the 5-nitro-isomer in alcohol, but less so in benzene; the 5-nitro-amine, on the other hand, is less soluble in benzene than the 3-nitro-amine, and separates from this solvent in either reddish-brown, stout, brittle needles or light yellow, soft plates.

3-*Nitro*-2-*aminoacetophenone.*—The acetamido-compound (1 g.) was heated for 1 hour at 95° with alcohol (20 c.c.), water (10 c.c.), and concentrated hydrochloric acid (10 c.c.), giving 3-nitro-2-aminoacetophenone as long golden-yellow needles, m. p. 95—96°, from aqueous alcohol (Found: N, 15·5. Calc. for $C_8H_8O_3N_2$: N, 15·55%); Bamberger (*loc. cit.*) gives m. p. 93°. For proof of structure, the nitro-amine (100 mg.) was reduced with iron powder (0·3 g.), acetic acid (2 c.c.), and water (2 c.c.) by the method previously described (*J.*, 1945, 646); the product, isolated with ether, was refluxed with phenanthraquinone (*ca.* 20 mg.) in alcohol (4 c.c.), and the phenazine was crystallised from acetic acid, giving yellow needles, m. p. 226—227° alone and when mixed with the sample previously described (*loc. cit.*).

8-*Nitro*-4-*hydroxycinnoline.*—A cold solution of 3-nitro-2-aminoacetophenone (0·45 g.) in acetic acid (4·5 c.c.) was treated with 1·5 c.c. of a mixture of concentrated sulphuric acid (5 c.c.) and water (1 c.c.). Powdered sodium nitrite (0·2 g.) was then added in portions, after which the mixture was heated on the steam-bath until it gave only a weak coupling reaction (½ hour). The solid (0·25 g.) obtained by dilution with water (2 vols.) was filtered off, washed, and recrystallised from alcohol, from which 8-nitro-4-hydroxycinnoline separated in brown needles, m. p. 185·5—186·5° alone and mixed with the sample described by Schofield and Simpson (*loc. cit.*).

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Warrington Yorke Department of Chemotherapy,
Liverpool School of Tropical Medicine.

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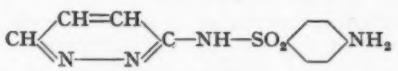
56. *The Conversion of Sucrose into Pyridazine Derivatives. Part I. 3-Sulphanilamido-6-methylpyridazine.*

By W. G. Overend and L. F. Wiggins.

The synthesis of 3-amino-6-methylpyridazine from lævulic acid is described. The preparation of the sulphanilamide derived from it has been achieved and its chemotherapeutic properties are discussed. Some structural aspects of the pyridazone intermediates are also mentioned.

Sulphanilamide derivatives of six-membered ring diazines have achieved marked success as chemotherapeutic agents for use in combating certain bacterial infections, but the diazine molecules used have been those of the pyrimidine and pyrazine series only. It seems that only one sulphanilamide derivative of pyridazine, namely 3-sulphanilamidopyridazine (I), has been described fully. This compound was prepared and its chemotherapeutic properties described by Anderson, Faith, Musson, Roblin, and Winneck (*J. Amer. Chem. Soc.*, 1942, **64**, 2902) who obtained it *via* Gabriel's 3-chloropyridazine (*Ber.*, 1909, **42**, 655). 3-Sulphanilamidopyridazine possessed high bacteriostatic activity *in vitro*, was capable of being absorbed strongly, and could be obtained in high concentration in the blood stream, but unfortunately and unexpectedly its activity *in vivo* was extremely low.

(I.)  $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO_2H$ (II.)

We have been interested in the pyridazine and pyridazone derivatives that can be obtained from lævulic acid (II), and in this paper is described the synthesis from this raw material of another sulphanilamide derivative of pyridazine, namely 3-*sulphanilamido*-6-*methylpyridazine* (IX),* together with the results of our investigations on the intermediate compounds used in this synthesis.

The new sulphanilamido-compound was found to possess high bacteriostatic activity in routine bacteriostatic tests—in fact it showed considerably greater activity than sulphathiazole with which it is compared in Table I. Moreover in its solubility (61) and that of its *N*-acetyl

Table I.

	Blood medium.	Broth medium.					Synthetic medium.		
Compound.	*Str. Hæmolyticus.*	*Str. Hæmolyticus.*	*B. Coli.*	*Pseudomonas æruginosa.*	*Staph. aureus.*	*Clostridium Welchii.*	*B. Coli.*	*Pseudomonas æruginosa.*	*Staph. aureus.*
3-Sulphanilamido-6-methylpyridazine	0·06	7	0·5	20	500	0·5	0·05	0·5	1·0
Sulphathiazole	0·3	15	5	5	100	5	0·03	7	2·0

The figures represent mg. of compound/100 c.c. necessary to prevent growth of the organism.

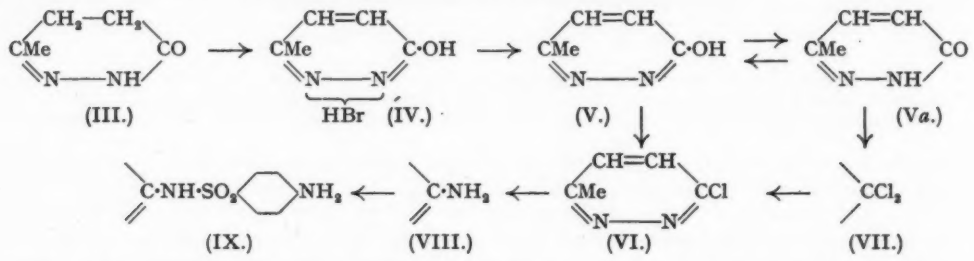
derivative (39) it appeared to offer advantages over sulphathiazole (40) and its *N*-acetyl derivative (3·3) (solubilities in parentheses in mg./100 c.c. of solution). More extensive biological work on this compound is in progress and the results will be published elsewhere.

Ethyl lævulate was condensed with hydrazine hydrate, either at room temperature or by heating for a short time, and 6-methyl-3-pyridazinone (III) was obtained in almost quantitative yield. This compound was first obtained by Curtius (*J. pr. Chem.*, 1894, **50**, 522) who believed he had obtained the hydrazide of lævulic acid until the true position was demontrated by Wolff (*Annalen*, 1912, **394**, 98). This substance could also be obtained by dry distillation of ethyl lævulate semicarbazone.

The 6-methyl-3-pyridazinone (III) was then converted into the corresponding pyridazone. This operation was first carried out by Poppenberg (*Ber.*, 1901, **34**, 3263) who treated 6-methyl-3-pyridazinone with bromine in acetic acid solution. Poppenberg obtained 6-methyl-3-pyridazone of m. p. 143° directly from this solution and made no mention of any other product

* While tests on this compound were being carried out, a patent (B.P. 563,629) granted to the American Cyanamide Co. was published in which this compound and others were described, although no details as to its preparation other than the introduction of the sulphanilamide residue to the pyridazine nucleus were given.

of the reaction. We, however, could not repeat the experiment as described by this author, and in fact we found the reaction was much more complicated.



When 6-methyl-3-pyridazinone was treated with bromine according to Poppenberg's conditions, hydrazine hydrobromide first separated, and after this had been removed a compound which clearly possessed salt-like properties crystallised out. This was *6-methyl-3-pyridazone monohydrobromide* (IV) and was obtained in 76% yield. The mother liquors gave a product soluble in ether which was identified as βδ-dibromolævulic acid. It was clear that during the bromine treatment, which amounts to a dehydrogenation, part of the 6-methyl-3-pyridazinone had suffered cleavage, giving hydrazine, isolated as its hydrobromide, and lævulic acid, which in the presence of bromine is converted into the dibromo-derivative.

The dehydrogenation was then carried out under different conditions, so as to try to eliminate cleavage of the diazine ring. Table II shows the results of these experiments, from which it is seen that when the reaction is carried out under anhydrous conditions, no secondary reaction occurs, and an almost theoretical yield of 6-methyl-3-pyridazone hydrobromide was obtained.

TABLE II.

Experimental conditions.	Hydrazine dihydrobromide.	6-Methyl 3-pyridazone monohydrobromide.	βδ-Dibromolævulic acid.
According to Poppenberg (*loc. cit.*)	28·8	111·9 (76·6%)	47·6
Bromine in acetic acid at room temp.	48·4	92·6 (63·5%)	74·5
Bromine in acetic acid at 0°	67·0	76·6 (52·5%)	93·8
Bromine in acetic acid (anhydrous conditions)	Nil	145·4 (99·5%)	Nil

The figures given refer to g. of each compound obtained from 100 g. of 6-methyl-3-pyridazinone monohydrate.

The decomposition of 6-methyl-3-pyridazone hydrobromide to the free base can be carried out under a variety of conditions. The hydrobromide is readily decomposed by sodium acetate solution, by liquid ammonia, or merely by boiling water. We have obtained the best yields by using the second method. The resulting *6-methyl-3-pyridazone* (V or Va) can easily be reconverted into the hydrobromide or hydrochloride by treatment in dry alcohol with the appropriate hydrogen halide.

6-Methyl-3-pyridazinone was converted into the pyridazone derivative by two alternative methods. Paal and Koch (*Ber.*, 1903, **36**, 2538) and Paal and Kuhn (*ibid.*, 1907, **40**, 4598) had used nitrous acid to dehydrogenate compounds similar to that under discussion; 6-methyl-3-pyridazinone was therefore converted to the corresponding pyridazone by treatment with sodium nitrite and dilute acetic acid. More recently Borsche (*Annalen*, 1941, **548**, 74) had used chromium trioxide in acetic acid solution to dehydrogenate similar compounds. When 6-methyl-3-pyridazinone was treated with these reagents it was converted into 6-methyl-3-pyridazone, but only in very poor yield.

The next step in the synthesis of the sulphanilamide required the preparation of 3-chloro-6-methylpyridazine (VI). Poppenberg (*loc. cit.*) had obtained this by chlorination of 6-methyl-3-pyridazone with phosphoryl chloride, but recorded no yield. We have found that this reaction could be carried out in such a way as to give the 3-chloro-derivative in 95% yield. In addition we tried an alternative method. Phosphorus pentachloride with anhydrous 6-methyl-3-pyridazone gave a product which although not clearly defined was apparently 3 : 3-dichloro-6-methyldihydropyridazine (VII). This on distillation decomposed with elimination of hydrogen chloride giving 3-chloro-6-methylpyridazine. Alternatively, the 3 : 3-dichloro-compound (VII) could be decomposed with the formation of 3-chloro-6-methyl-

pyridazine by treatment with sodium hydroxide solution. However the yield of this material obtained by the last two methods did not compare with that obtained by the treatment of 6-methyl-3-pyridazone with phosphoryl chloride. The chloropyridazine gave a crystalline *monohydrochloride* and *monohydrobromide*, although Poppenberg (*loc. cit.*) stated that it did not form salts.

By treatment with aqueous ammonia at high temperature the 3-chloro-derivative was converted into 3-*amino*-6-*methylpyridazine* (VIII) in about 50% yield, but some 6-methyl-3-pyridazone was obtained also. With methyl alcoholic ammonia, a slightly higher yield (60%) of amine was obtained, together with a very small amount of 3-*methoxy*-6-*methylpyridazine*, identified as its *hydrochloride*, which was synthesised by treatment of 3-chloro-6-methylpyridazine with sodium methoxide.

3-Amino-6-methylpyridazine formed only mono-salts (a *hydrochloride* and a *picrate*). It also formed a beautifully crystalline *acetyl* derivative, which also formed only mono-salts (a *hydrochloride* and a *hydrobromide*).

To introduce the sulphanilamido-residue, we have used both the usual procedures. Thus the amine was condensed with *N*-acetylsulphanilyl chloride in pyridine solution, and 3-N-*acetylsulphanilamido*-6-*methylpyridazine* was obtained in 84% yield. It was possible to effect some condensation in chloroform, without the presence of another base—that is, by making use of the basic nature of the pyridazine ring for absorption of hydrogen chloride—but the yield was only 25%. The *N*-acetyl group was easily removed by hydrolysis with either aqueous sodium hydroxide or dilute hydrochloric acid, and 3-sulphanilamido-6-methylpyridazine (IX) obtained in 87% yield. (IX) formed a *dihydrochloride*.

The amine (VIII) was also condensed with *p*-nitrobenzenesulphonyl chloride in pyridine solution, but the yield of 3-p-*nitrobenzenesulphonamido*-6-*methylpyridazine* was only 46%, and reduction of this compound was accompanied by secondary reactions so that only a 21% yield of the sulphanilamide was obtained.

Experimental.

6-*Methyl*-3-*pyridazinone*.—(1) Ethyl lævulate (84·5 g.) and hydrazine hydrate (50/50 w/w, 55·7 g.) were mixed, and ethyl alcohol was added until a homogeneous mixture was obtained. The solution was boiled under reflux for 1 hour and then left overnight. The crystals which had separated were collected, and a second crop obtained on evaporation of the mother liquor. The product recrystallised from water in large colourless rhombs, m. p. 82°. Yield, 76 g. (practically quantitative). This was 6-methyl-3-pyridazinone monohydrate. A sample was dried in a vacuum at 110° and the resulting anhydrous compound recrystallised from benzene; it had 105° (Wolff, *loc. cit.*, gives m. p. 104—105°) (Found: C, 54·2; H, 6·7; N, 25·8. Calc. for $C_5H_6ON_2$: C, 53·6; H, 7·0; N, 25·0%).

(2) Ethyl lævulate semicarbazone (2·62 g.) was subjected to dry distillation. The distillate (1·03 g.) crystallised on cooling. It recrystallised from water in large rhombic crystals, m. p. 82° alone or in admixture with 6-methyl-3-pyridazinone obtained as above. Yield, 72%.

The Action of Bromine on 6-*Methyl*-3-*pyridazinone*.—(a) *Poppenberg's method* (*loc. cit.*). 6-Methyl-3-pyridazinone monohydrate (31·9 g.) was dissolved in warm glacial acetic acid (100 g.) and bromine (12·17 c.c.) was slowly added. Thereafter the mixture was heated at 100° for 15 minutes. Hydrazine hydrobromide (9·2 g.) [m. p. 207° (decomp.) after recrystallisation from glacial acetic acid] separated and was filtered off. By next day the filtrate had deposited 6-*methyl*-3-*pyridazone hydrobromide* (35·7 g.); after recrystallisation from glacial acetic acid this had m. p. 184·5—185°, and boiling water, boiling pyridine, or liquid ammonia decomposed it with formation of 6-methyl-3-pyridazone and bromide ions (Found: C, 31·5; H, 3·6; N, 14·4. $C_5H_7ON_2Br$ requires C, 31·4; H, 3·7; N, 14·7%). The mother liquors on evaporation yielded crude $\beta\delta$-dibromolævulic acid as a syrup (15·2 g.), which crystallised after long standing with alcohol; recrystallised from ligroin (b. p. 60—80°) it yielded shining white needles, m. p. 112—113°, not depressed in admixture with pure $\beta\delta$-dibromolævulic acid (Found: C, 21·6; H, 2·3. Calc. for $C_5H_6O_3Br_2$: C, 21·8; H, 2·1%).

(b) *At room temperature*. To 6-methyl-3-pyridazinone monohydrate (47·5 g.) dissolved in glacial acetic acid (125 c.c.) was slowly added bromine (37 c.c.) at room temperature. When 14 c.c. of the bromine had been added, minute crystals began to separate, and after completion of the addition the hydrazine hydrobromide (23 g.) was collected. The filtrate was kept overnight and the crystals of 6-methyl-3-pyridazone hydrobromide, which separated, were filtered off; ether added to the filtrate precipitated a second crop (total yield, 44 g.). The mother liquors were evaporated to a syrup of crude $\beta\delta$-dibromolævulic acid (32 g.).

(c) *Under ice-cold conditions*. 6-Methyl-3-pyridazinone monohydrate (20·0 g.) was dissolved in glacial acetic acid (60 c.c.) and the solution cooled in an ice-bath. Bromine (16 c.c.) was slowly added with shaking. When exactly half the bromine had been added hydrazine hydrobromide (13·4 g.) separated (at this stage hydrogen bromide was evolved). The filtrate after the removal of this was kept overnight; 6-methyl-3-pyridazone hydrobromide (13·5 g.) had then separated and was collected. Evaporation of the mother liquors gave a syrup of crude $\beta\delta$-dibromolævulic acid (18·8 g.).

Dehydrogenation of 6-*Methyl*-3-*pyridazinone under Anhydrous Conditions*.—6-Methyl 3-pyridazinone monohydrate (165 g.) was dehydrated by heating at 120°/15 mm. for 4 hours. The anhydrous product was dissolved in freshly distilled glacial acetic acid (350 c.c.), and bromine (110·5 c.c.) slowly added at room temperature without cooling. No hydrazine hydrobromide separated. The solution was kept

overnight; crystals had then separated, and were collected. A further crop was obtained by addition of ether to the mother liquors. The combined products had m. p. 184° and were practically pure 6-methyl-3-pyridazone monohydrobromide. Yield, 240 g. (quantitative).

6-*Methyl*-3-*pyridazone Monohydrate*.—(*a*) 6-Methyl-3-pyridazone monohydrobromide (22·4 g.) was suspended in glacial acetic acid (85 c.c.) and freshly fused and powdered sodium acetate (13·5 g.) added. The mixture was heated under reflux for 1 hour, evaporated to dryness, and the residue extracted with boiling chloroform. The extracts were dried ($MgSO_4$), the chloroform was removed by evaporation, and the residue, 6-methyl-3-pyridazone, recrystallised from water as the *monohydrate*, m. p. 119—123°. Yield, 12·9 g.; 86% (Found: C, 47·3; H, 6·1. $C_5H_6ON_2,H_2O$ requires C, 46·9; H, 6·3%).

(*b*) 6-Methyl-3-pyridazone monohydrobromide (1·14 g.) was dissolved in cold water, and a solution containing sodium hydroxide (1 mol., 0·24 g.) added. After evaporation to dryness the residue was extracted with chloroform, and 6-methyl-3-pyridazone monohydrate isolated as above. Yield, 0·47 g.; 72%.

(*c*) 6-Methyl-3-pyridazone monohydrobromide (5·04 g.) was dissolved in liquid ammonia (100 c.c.) and the solution allowed to evaporate overnight under anhydrous conditions. The residue was extracted with ether, and after removal of the solvent 6-methyl-3-pyridazone was obtained as above. Yield, 3·4 g.; 82%.

(*d*) 6-Methyl-3-pyridazone monohydrobromide (1 g.) was dissolved in water (10 c.c.) and the solution was boiled. Thereafter it was neutralised with silver carbonate, filtered, and evaporated to dryness. The residue was extracted with chloroform, and the extract, after being dried ($MgSO_4$), was evaporated to dryness. 6-Methyl-3-pyridazone was obtained after recrystallisation from water. Yield, 0·55 g.; 82%.

The monohydrate was dehydrated by heating it at 120° for 2 hours in a vacuum. The resulting anhydrous *compound*, m. p. 138°, crystallised from acetone in colourless needles (Found: C, 54·2; H, 5·7; N, 25·9. $C_5H_6ON_2$ requires C, 54·5; H, 5·4; N, 25·4%).

(*e*) 6-Methyl-3-pyridazinone (2·84 g.) was dissolved in glacial acetic acid (25 c.c.) and chromium trioxide (2·2 g.) was added to the solution. The mixture was kept overnight, and the pasty mass extracted with acetone. The solvents were removed from the extract and the solid residue was recrystallised from water; colourless plates (0·6 g., 20%), m. p. 120—123°, alone or in admixture with 6-methyl-3-pyridazone monohydrate.

(*f*) 6-Methyl-3-pyridazinone monohydrate (3·22 g.) was dissolved in water (50 c.c.) and sodium nitrite (1·8 g.) followed by dilute acetic acid was added. Next day the mixture was evaporated to dryness, and the residue extracted with acetone. The extract was dried ($MgSO_4$) and the solvent removed. The residue was recrystallised from water; white plates (0·03 g., 10%), m. p. 120—123° alone or in admixture with 6-methyl-3-pyridazone monohydrate.

6-*Methyl*-3-*pyridazone Monohydrochloride*.—Anhydrous 6-methyl-3-pyridazone (0·1 g.) was dissolved in absolute alcohol (5 c.c.) and the solution cooled to 0°, and treated with dry hydrogen chloride. The *hydrochloride* separated as a white solid; this was filtered off and recrystallised from dry alcohol–ether; m. p. 176—176·5° (Found: C, 41·5; H, 4·7. $C_5H_7ON_2Cl$ requires C, 41·0; H, 4·8%).

The hydrobromide was prepared in the same way. It had m. p. 183—184° and was identical with the product of the treatment of 6-methyl-3-pyridazinone with bromine (Found: C, 31·1; H, 3·4; N, 14·4%.

3-*Chloro*-6-*methylpyridazine*.—(*a*) Anhydrous 6-methyl-3-pyridazone (19·4 g.) was heated with phosphorus oxychloride (75 c.c.) at 100° for 30 minutes. The excess of phosphorus oxychloride was removed by distillation and crushed ice carefully added to the residue. The product was made alkaline to brilliant-yellow with 5N-sodium hydroxide. Thereafter it was exhaustively extracted with ether, the ether extracts were dried ($MgSO_4$), and the solvent was removed. The solid which remained was recrystallised from ligroin (b. p. 40—60°); shining white needles, m. p. 58° (yield, 19·4 g., 96%).

(*b*) Anhydrous 6-methyl-3-pyridazone (6·8 g.; 1 part) and phosphorus pentachloride (34 g.; 5 parts) were intimately mixed and heated on an oil-bath at 100° for 1 hour. Hydrogen chloride was evolved. After being allowed to cool, crushed ice was added, and the product made alkaline with sodium hydroxide solution. Thereafter it was extracted with chloroform and the extract dried ($MgSO_4$), filtered, and evaporated to a brown liquid (*A*) (6·8 g.) which was probably 3 : 3-dichloro-6-methyldihydropyridazine. This on attempted distillation at 150° (bath temperature)/15 mm. decomposed, and crystals of 3-chloro-6-methylpyridazine monohydrochloride appeared in the distillate.

The liquid (*A*) (1·3 g.) and 10% sodium hydroxide solution (10 c.c.) were boiled under reflux for 0·5 hours, filtered (charcoal), and the filtrate extracted with ether. The extract was dried ($MgSO_4$), filtered, and the solvent removed. There remained a solid which recrystallised from ligroin and had m. p. 58° alone or in admixture with 3-chloro-6-methylpyridazine. Yield, 0·25 g.; 26%.

3-*Chloro*-6-*methylpyridazine Monohydrobromide*.—3-Chloro-6-methylpyridazine (0·1 g.) was dissolved in absolute alcohol (3 c.c.), the solution cooled in ice, and dry hydrogen bromide passed in to precipitate the *hydrobromide* which recrystallised in long pink needles, m. p. 220° (decomp.) (Found: N, 13·5; total halide, 54·5. $C_5H_6N_2ClBr$ requires N, 13·4; total halide, 55·1%). The *monohydrochloride*, prepared similarly, separated from alcohol–ether in slightly pink needles, m. p. 250° (with darkening) (Found: N, 16·4. $C_5H_6N_2Cl_2$ requires N, 16·8%).

3-*Amino*-6-*methylpyridazine*.—(*a*) 3-Chloro-6-methylpyridazine (17·25 g.) was dissolved in dry methyl alcohol (1 l.) saturated at 0° with ammonia, and the solution heated at 175° for 2 days in an autoclave. The solution was then filtered and concentrated in a vacuum. The residue was treated with barium hydroxide (31·7 g. in 250 c.c. of water) at 80° in an atmosphere of nitrogen. The solution was evaporated to dryness and the residue extracted once with benzene (Extract *A*) and then with chloroform (Extract *B*). All these later operations were conducted in an atmosphere of nitrogen.

Extract *A* was dried ($CaCl_2$), and the solvent removed. A moist residue remained, which was extracted with warm water. The solid dissolved, and from the solution 3-amino-6-methylpyridazine was isolated, m. p. 225°. Yield, 4·4 g. A brown liquid did not dissolve in the water, and this was separated and dried. It was then dissolved in absolute ethyl alcohol, and dry hydrogen chloride was

bubbled through the solution. On addition of ether, a solid separated and was collected (0·2 g.). After recrystallisation from ethyl alcohol it had m. p. 131—132° not depressed in admixture with an authentic specimen of 3-methoxy-6-methylpyridazine monohydrochloride. Hence it appeared that the brown oil was 3-methoxy-6-methylpyridazine.

Extract *B* was dried ($MgSO_4$) and the solvent was removed. The solid residue of 3-amino-6-methylpyridazine (8·9 g., 60%) recrystallised from water in white rhombs, m. p. 224—225°. It was basic, soluble in alcohol and water, slightly soluble in chloroform, but insoluble in ether. It formed a complex with silver nitrate which was decomposed by nitric acid (Found: C, 55·2; H, 6·2; N, 38·2. $C_5H_7N_3$ requires C, 55·0; H, 6·4; N, 38·3%). The *monohydrochloride*, prepared by the action of dry hydrogen chloride in ice-cold solution, separated from alcohol in colourless plates, m. p. 237° (Found: C, 41·6; H, 5·40. $C_5H_8N_3Cl$ requires C, 41·2; H, 5·5%). The *monopicrate* separated from alcohol in yellow needles, m. p. 220—221° (Found: C, 38·8; H, 3·3; N, 25·2. $C_{11}H_{10}O_7N_6$ requires C, 39·1; H, 2·9; N, 24·9%).

(*b*) 3-Chloro-6-methylpyridazine (4·1 g.) was heated at 150° for two days with ammonia (*d*, 0·88) in an autoclave. Thereafter the solution was filtered (charcoal), evaporated to dryness, and the residue dissolved in water and treated with sodium hydroxide (1 mol.) at 100° for 1 hour. The solution was acidified with dilute hydrochloric acid and evaporated to dryness. The thoroughly dried residue was extracted with chloroform (*A*) and then with alcohol (*B*).

Extract *A* was evaporated to dryness; the residue recrystallised from water in white plates of 6-methyl-3-pyridazone, m. p. 123—124° (1 g., 28·6%).

Extract *B* was evaporated to dryness; the residue of 3-amino-6-methylpyridazine hydrochloride was dissolved in the minimum amount of water, cooled to 0°, and made alkaline with sodium hydroxide. The solution was filtered (charcoal) and kept overnight. The crystals which had separated were 3-amino-6-methylpyridazine, m. p. 225° (1·7 g., 48·5%).

3-Methoxy-6-methylpyridazine.—3-Chloro-6-methylpyridazine (2·0 g.) was dissolved in dry methyl alcohol (150 c.c.), containing sodium (5 g.), and the solution boiled under reflux for 2 hours. After evaporation to dryness, excess of aqueous potassium hydroxide was added, and the resulting solution extracted with benzene. The extract was dried ($MgSO_4$) and the benzene removed. The *methoxy*-compound (0·70 g., 36·8%) distilled as a colourless liquid which soon turned red; b. p. 210°, $n_D^{21°}$ 1·5014 (Found: N, 22·5. $C_5H_8ON_2$ requires N, 22·6%). Much red polymer remained in the flask. The *hydrochloride*, prepared by the action of dry hydrogen chloride in ice-cold solution, crystallised from ethyl alcohol in large colourless deliquescent plates, m. p. 137—138° (Found: C, 44·6; H, 5·8. $C_6H_9ON_2Cl$ requires C, 44·8; H, 5·6%).

3-Acetamido-6-methylpyridazine.—3-Amino-6-methylpyridazine (0·3 g.) was boiled for 15 minutes with fused sodium acetate (0·4 g.) and acetic anhydride (5 c.c.). Thereafter the solution was poured into water, and the solution neutralised with sodium bicarbonate and extracted with chloroform. The extract, after being dried ($MgSO_4$), was evaporated to dryness and the residual *acetyl* derivative recrystallised from water. Yield, 0·31 g. (45%), m. p. 214—215° (Found: C, 55·5; H, 5·9; N, 27·8. $C_7H_9ON_3$ requires C, 55·6; H, 5·9; N, 27·8%). The *monohydrochloride*, prepared by the action of dry hydrogen chloride in alcoholic solution, crystallised from alcohol–ether in white plates, m. p. 235° (decomp.) (Found: Cl, 18·9. $C_7H_{10}ON_3Cl$ requires Cl, 18·9%). The *monohydrobromide*, which was unstable, formed crystals, m. p. 206° (Found: Br, 36·6. $C_7H_{10}ON_3Br$ requires Br, 36·2%).

3-N-Acetylsulphanilamido-6-methylpyridazine.—(*a*) *N*-Acetylsulphanilyl chloride (2·88 g., 1·1 mols.) in dry pyridine (20 c.c.) was added to a suspension of 3-amino-6-methylpyridazine (1·354 g., 1 mol.) also in dry pyridine. The mixture was kept at room temperature for 24 hours, and then poured into water containing sodium hydroxide (0·5 g., 1 mol.) and concentrated. The *compound* separated as a yellow solid which recrystallised from acetic acid–water in white cubes, which turned pink on standing; m. p. 247—247·5° (Found: C, 51·0; H, 4·7; N, 18·4. $C_{12}H_{14}O_3N_4S$ requires C, 51·0; H, 4·6; N, 18·3%). Yield, 3·2 g. (84%). Solubility in water at 15°, 39 mg./100 c.c. of solution.

(*b*) 3-Amino-6-methylpyridazine (0·48 g.) was dissolved in dry chloroform (20 c.c.) and to the solution was added *N*-acetylsulphanilyl chloride (1·1 g.) also in dry chloroform (10 ml.). The mixture was kept at 45° for 30 minutes. The chloroform was removed, and sodium hydroxide (0·18 g.) in water (10 c.c.) were added. On concentrating the solution an oil separated, which crystallised. After recrystallisation from acetic acid–water it had m. p. 247° alone or in admixture with 3-*N*-acetylsulphanilamido-6-methylpyridazine. Yield, 0·30 g. (22·3%).

3-Sulphanilamido-6-methylpyridazine.—(*a*) 3-*N*-Acetyl-6-methylsulphanilamidopyridazine (1·9 g.) was dissolved in aqueous sodium hydroxide solution (0·7 g. in 7 c.c.) and the mixture heated under reflux for 45 minutes. It was then allowed to cool, filtered (charcoal), and made just acid with dilute hydrochloric acid. The solid which then separated was recrystallised from hot water; yellow needles, m. p. 195—196° (Found: C, 50·2; H, 4·3; NH_2 (nitrite titration), 6·0. $C_{11}H_{12}O_3N_4S$ requires C, 50·0; H, 4·5; NH_2, 6·1%). Yield, 1·45 g. (87%). The *dihydrochloride*, prepared by the action of dry hydrogen chloride in alcoholic solution, crystallised from alcohol–water in white plates, m. p. 215° (Found: C, 39·3; H, 3·9. Cl, 11·8. $C_{11}H_{14}O_3N_4Cl_2S$ requires C, 39·3; H, 3·9; Cl, 11·8%).

(*b*) 3-*N*-Acetyl-6-methylsulphanilamidopyridazine (0·03 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (7 c.c.). When cool, the solution was neutralised with sodium hydroxide solution. A yellow solid separated and was collected. After recrystallisation from water it had m. p. 195—196°, alone or in admixture with 3-sulphanilamido-6-methylpyridazine. Yield, 0·02 g. (80%). Solubility in water at 15°, 61 mg./100 c.c. of solution.

(*c*) 3-Amino-6-methylpyridazine (0·37 g.) suspended in dry pyridine was treated with *p*-nitrobenzenesulphonyl chloride (0·82 g., 1·1 mols.), dissolved in dry pyridine, at 0°. After 24 hours at room temperature, water containing sodium hydroxide (0·13 g., 1 mol.) was added, and the mixture evaporated until a solid began to separate. This 3-p-*nitrobenzenesulphonamido-6-methylpyridazine* was collected and recrystallised from alcohol–water; pale yellow crystals, m. p. 161° (Found: C, 44·5; H, 3·3. $C_{11}H_{10}O_4N_4S$ requires C, 44·8; H, 3·4%). Yield, 0·47 g. (46%).

The above nitro-compound (0·39 g.) was dissolved in dry methyl alcohol (150 c.c.) and hydrogenated

over Raney nickel at room temperature. After being filtered the solution was evaporated. The residue was dissolved in water, filtered (charcoal), and allowed to cool; a yellow solid then separated, m. p. 196—197°, alone or in admixture with 3-sulphanilamido-6-methylpyridazine. Yield, 0·07 g. (21%). A brown oil was also formed which would not crystallise. The crystalline sulphonamide was readily converted by treatment with acetic anhydride–acetic acid into 3-*N*-acetylsulphilamido-6-methylpyridazine, m. p. 247°.

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THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, June 18th,* 1946.]

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57. *Acridine Syntheses and Reactions. Part III. Synthesis of Amino-acridines from Formic Acid and Amines.*

By ADRIEN ALBERT

The mechanism of the condensation of *m*-phenylenediamine with formic acid to give proflavine (2 : 8-diaminoacridine) was investigated in Parts I and II (Albert, *J.*, 1941, 121, 484). A study of the scope of this synthesis, using a variety of amines, now shows it to be a most useful method for preparing symmetrically substituted derivatives of proflavine.

THE following examples of the reaction of oxalic (and/or formic) acid with diamines to give yellow dyes are in the patent literature: (i) with *m*-tolylenediamine to give an un-named product (CIBA, F.P. 203,467, 1890); (ii) with *m*-aminodimethylaniline, *m*-aminodiethylaniline, *m*-aminoethylaniline, *m*-aminomethyl-*o*-toluidine, and *m*-aminoethyl-*o*-toluidine to give un-named acridine dyes (Leonhardt, D.R.-P. 67,126, 1890); (iii) with *m*-phenylenediamine to give proflavine (Poulenc, D.R.-P. 347,819, 1921); (iv) with *N*-(diethylaminoethyl)-*m*-phenylenediamine to give 2 : 8-bis(diethylaminoethylamino)acridine (I.G. Farben., D.R.-P. 488,890, 1924); (v) with 2 : 4-diamino-anisole or -phenetole to give 3 : 7-dimethoxy- or -diethoxy-proflavine (B.D. Corp., B.P. 248,282, 1926).

In Parts I and II (*locc. cit.*), conditions for the synthesis of proflavine from *m*-phenylenediamine were explored and the reaction was shown to proceed *via* *m*-aminoformanilide and tetra-aminobenzhydrol (yield, 60%). As no other use of the reaction is recorded in the general literature, a survey of its scope and probable usefulness has been attempted.

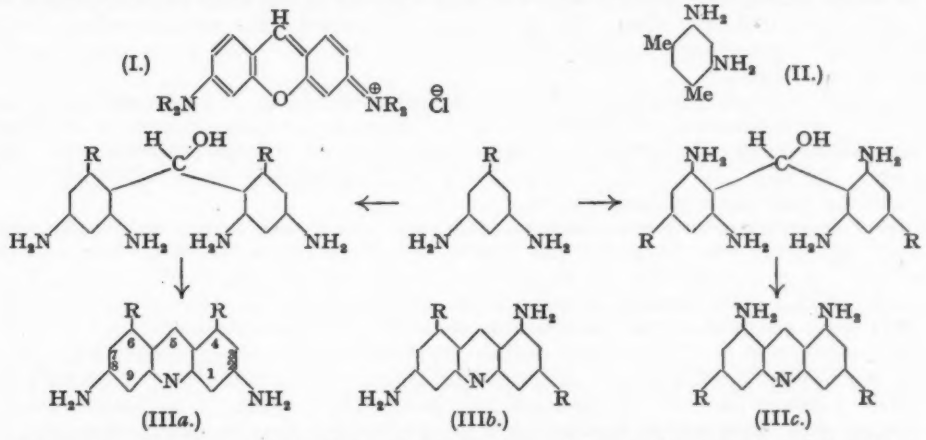
Amines other than m-*Diamines.*—No acridines were obtained when the conditions optimal for *m*-phenylenediamine were applied to the following amines, which were recovered unchanged or in the form of their formyl or oxalyl derivatives: aniline, *p*-phenylenediamine, *p*-toluidine, *m*-toluidine, *m*-anisidine, *m*-chloroaniline, *m*-nitroaniline, *m*-aminobenzoic acid, and metanilic acid. No improvement resulted on increasing the severity of the conditions (4 hours at 200° instead of ¾ hour at 155°) or by varying the amount of hydrogen chloride between 0 and 2 molecules per molecule of amine. *o*-Phenylenediamine gave benziminazole (with formic acid) and a tetracyclic compound, fluoflavine (with oxalic acid, cf. Hinsberg and Pollak, *Ber.*, 1896, 29, 784).

m-Aminophenol could conceivably react in three ways, losing ammonia or water to give (i) 2 : 8-dihydroxyacridine, (ii) 2-amino-8-hydroxyacridine, or (iii) 2 : 8-diaminoxanthylium chloride (I, R = H). Since *N*-acylation takes precedence over *O*-acylation, the first intermediate should be *m*-hydroxyformanilide (cf. Part II), and possibility (iii) is rendered unlikely. Actually, no (I) was formed, the principal product being a *complex* of two molecules of 2-amino-8-hydroxyacridine and one of 2 : 8-dihydroxyacridine. *m*-Diethylaminophenol, which cannot give an acridine, produced Pyronine B (I, R = Et) in good yield; this constitutes a new xanthen synthesis.

The failure of *m*-toluidine and *m*-anisidine to give acridines with formic acid reveals that a high electron density *ortho* to an amino-group is a prerequisite for this reaction; the failure of *p*-toluidine stands in contrast to its ready reaction with formaldehyde and mineral acid to give 3 : 7-dimethylacridan (Ullmann, *Ber.*, 1903, 36, 1018).

These results indicate that the main usefulness of the reaction under consideration will be confined to *m*-diamines.

N-*Substituted* m-*Diamines.*—*m*-Aminodimethylaniline was condensed with oxalic acid to give a 60% yield of acridine-orange (2 : 8-bisdimethylaminoacridine) identified by its having



the same properties as, and not depressing the m. p. of, a specimen prepared by the action in turn of formaldehyde, hydrochloric acid, and ferric chloride on the same amine (Biehringer, *J. pr. Chem.*, 1896, **54**, 241). A cream-coloured by-product (3% yield) proved to be *bis*-m-*dimethylamino-oxanilide*, confirmed by its synthesis from *m*-aminodimethylaniline and oxalyl chloride. That this compound is a by-product and not an intermediate was shown by its failure to give an acridine when heated with zinc chloride and glycerol. As formic acid had proved somewhat superior to oxalic acid up to this point, the use of the latter was abandoned in the remainder of this survey.

3-Aminodiphenylamine gave a 40% yield of 2 : 8-*bisphenylaminoacridine* and a by-product, m. p. 217°, which proved to be 2-aminoacridine.

C-*Substituted* m-*Diamines.*—It was shown (Part II) that *m*-phenylenediamine could conceivably yield three isomerides, *viz.*, 2 : 8-, 2 : 6-, and 4 : 6-diaminoacridine (III*a*, *b*, and *c*; R = H), but only the 2 : 8-isomeride (proflavine) is actually produced. It is now found that 4 : 6-diamino-*m*-xylene (II), which could give only 4 : 6-diamino-1 : 3 : 7 : 9-tetramethylacridine, does not react at all. It seems that there is little or no tendency for the carbon bridge between the two benzene rings to be formed by an attack on the 2-position.

In the case of 1 : 3-diamines with a substituent in the 2-position, the formation of isomerides is physically impossible. 2 : 6-Tolylenediamine gave 2 : 8-*diamino*-1 : 9-*dimethylacridine* (57% yield), characterised as its *monoacetyl* derivative, and some by-products, not obtained pure, resembling the family of diacridyl ethers described in Part I.

In the case of 1 : 3-diamines having a substituent in the 5-position, there are the same possibilities of formation of isomerides as with *m*-phenylenediamine. However, only one product analysing for a diaminodimethylacridine was isolated from 3 : 5-tolylenediamine. It was a fairly strong base ($pK_a = 10{\cdot}1$ in 50% ethanol at 20°) with yellow salts and, for the reason given above, was assigned the constitution 2 : 8-*diamino*-4 : 6-*dimethylacridine* (III*a*; R = Me). Data obtained in the determination of pK_a values for 120 acridines (Albert and Goldacre, *J.*, 1946, 706) enable the following values to be predicted for (III*a*, *b*, and *c*) respectively: 10·0, 9·1, and 6·6 (all $\pm$ 0·5). This confirmatory evidence may be supplemented by the strong likelihood that a 4 : 6-diamine (such as III*c*) would have blue or green salts (Albert and Bird, *J. Soc. Dyers and Col.*, 1943, **59**, 74, and unpublished work). 3 : 5-*Diaminoanisole* was prepared for use in this reaction, but underwent demethylation during the condensation which resulted in an intractable mixture. 3 : 5-Diaminobenzoic acid gave a 65% yield of a diaminoacridinedicarboxylic acid (probably 2 : 8-4 : 6-). This resisted decarboxylation, a process which could have confirmed the orientation.

1 : 3-Diamines having a substituent in the 4-position can conceivably give rise to six isomerides; for example, 2 : 4-tolylenediamine could give (i) 2 : 8-diamino-3 : 7-dimethylacridine, (ii) 2 : 6-diamino-3 : 9- (and 3 : 7-) dimethylacridines, and (iii) 4 : 6-diamino-1 : 7- (and 1 : 9- and 3 : 7-) dimethylacridines. Groups (ii) and (iii) are excluded by the results obtained with 4 : 6-diamino-*m*-xylene (see above). In each of the following cases, only one disubstituted diaminoacridine could be isolated and the pK_a values were consistent with the amino-

groups being in the 2 : 8-positions. 2 : 4-Tolylenediamine gave a 75% yield of acridine-yellow (2 : 8-diamino-3 : 7-dimethylacridine) identical with the product obtained by the action in turn of formaldehyde, hydrochloric acid, and ferric chloride on the same amine (Ullmann and Fitzenkam, *Ber.*, 1905, **38**, 3794). No m. p. has been recorded for acridine-yellow; it was found to be 325° (quite sharp) for specimens prepared by either route and no depression occurred when they were mixed.

Likewise 2 : 4-diaminoanisole, 2 : 4-diaminophenetole and chloro-2 : 4-diaminobenzene gave respectively 2 : 8-*diamino*-3 : 7-*dimethoxy*-, 2 : 8-*diamino*-3 : 7-*diethoxy*-, and 3 : 7-*dichloro*-2 : 8-*diamino-acridine*. The yields were only moderate, and diacridyl ethers were simultaneously formed. 3 : 7 : 3′ : 7′-*Tetrachloro*-2 : 8 : 2′ : 8′-*tetra-amino*-5 : 10-*dihydrodiacridyl* 5 : 5′-*ether* was obtained analytically pure.

When 2-dimethylamino-*p*-toluidine was condensed with formic acid, 2 : 8-*bismethylamino*-3 : 7-*dimethylacridine* was obtained. The loss of two *N*-methyl groups under hot, acid conditions may be connected with the serious clashing of van der Waals radii (*N*-methyl with *C*-methyl) which a scale drawing reveals. Lewis and Bigeleisen (*J. Amer. Chem. Soc.*, 1943, **65**, 1144) draw attention to the considerable steric effect of an *ortho* methyl group upon a dimethylamino-group which is thereby thrown out of the plane of the (aromatic) ring.

Non-symmetrical Condensations.—Unsuccessful attempts were made to condense together two different amines under the above conditions (*m*-aminoformanilide, or *m*-phenylenediamine plus formic acid, with aniline hydrochloride or *p*-phenylenediamine dihydrochloride; also formanilide with *m*-phenylenediamine dihydrochloride). In each case proflavine was the only acridine formed, usually in good yield, thus demonstrating the mobility of the formyl group under the experimental conditions. Similar results were obtained when substantially anhydrous conditions were used.

This led to the investigation of five patents which appeared to produce non-symmetrically substituted acridines from two different diamines, one of them formylated. In D.R.-P. 149,409 and 149,410 (Geigy, 1903) the amines are heated at 210—240° without solvent, using ammonium chloride or aniline hydrochloride as catalysts, and (un-named) acridines are said to be produced. Actually, no non-symmetrical acridine could be obtained by this method, *e.g.*, *m*-tolylenediamine and monoformyl-*m*-phenylenediamine (D.R.-.P. 149,409, example 2) gave only unidentified yellow resinous material of low basic strength with ammonium chloride as catalyst, plus some acridine-yellow when aniline hydrochloride was used. The same result was obtained when glycerol was used as a solvent at 150—190° (as in D.R.-.P. 161,699; Geigy, 1905). However, it seems that conditions may be more favourable when one reactant is a *m*-aminophenol because, on following example 4 from the latter patent (*m*-diethylaminophenol, condensed with diformyl-*m*-tolylenediamine and *m*-tolylenediamine dihydrochloride), a 14% yield of 2-*amino*-8-*diethylamino*-3-*methylacridine* was obtained.

The production of non-symmetrically substituted derivatives of proflavine by condensing equimolecular amounts of a diamine and the dihydrochloride of another diamine, one of them formylated (in glycerol at 185—190°), is claimed in D.R.-P. 292,848 and 346,961 (AGFA, 1915), no extraneous catalyst being used. The most important example in these patents would appear to be the condensation of 2-dimethylamino-*p*-toluidine dihydrochloride with 2-*amino*-4-*formamidotoluene* (from 2-*nitro*-4-*formamidotoluene*). This example claims to give 2-amino-8-dimethylamino-3 : 7-dimethylacridine which can be methylated in the 10-position to give the antibacterial drug, Flavicid (AGFA, D.R.-P. 366,096, 1921) which had already been withdrawn from use when Wagner wrote: " The non-symmetrical structure prevents uniformity in manufacture " (*Z. Immunitätsforsch.*, 1938, **94**, 171). In attempting to reproduce this example, a 35% yield of a symmetrical product (acridine-yellow) and a 20% yield of 2-*amino*-8-*methylamino*-3 : 7-*dimethylacridine* were obtained, a methyl group being lost from 2-dimethylamino-*p*-toluidine as before.

Two patents claiming to condense 2-naphthylamine similarly with diamines to give aminobenzacridines gave only symmetrical products derived from the diamine (AGFA, D.R.-PP. 346,962 and 346,963, 1915).

Conclusions.—The reaction between *m*-diamines and formic acid is the most direct and useful method for producing symmetrically substituted acridines carrying amino-groups in the 2- and 8-positions. Only one operation is involved and the mechanism is now fairly well understood. Yields lie between 20 and 75% and mixtures of isomerides are not formed as in some alternative syntheses. The reaction is not very successful in producing non-symmetrically substituted acridines and fails when acetic or benzoic acid is substituted for formic acid.

The diaminoacridines described in this work have marked anti-bacterial properties (cf. Albert, Rubbo, Goldacre, Davey, and Stone, *Brit. J. Exper. Path.*, 1945, **26**, 160).

Experimental.

Standard Conditions.—Unless otherwise specified, the condensation was carried out by heating the amine (0·1 mol.), formic acid (0·05 mol., anhydrous), hydrogen chloride (0·115 mol., in the form of standardized concentrated acid), and glycerol (three times the weight of the amine) to 155° (internal) during ½ hour and maintaining this temperature a further ½ hour. The best results were obtained in an open vessel of cross-section area 1·5 sq. cm. per g. of amine, with continuous, gentle stirring. Where zinc chloride is specified, an amount equal to 1·5 times the weight of the amine was used.

m-*Aminophenol.*—This was condensed under the standard conditions. The melt was boiled with twice its volume of water, cooled, made neutral with sodium bicarbonate, and filtered (yield, 67% total acridines; colourless filtrate indicates absence of xanthylium salts). The precipitate was boiled with 0·5N-hydrochloric acid and cooled. 2 : 8-Dihydroxyacridine hydrochloride, deposited in 5% yield, was identified by comparison with a sample made from proflavine (Benda, *Ber.*, 1912, **45**, 1794) and conversion to the dimethyl ether, m. p. and mixed m. p. 138° (Cassella, D.R.-P. 392,066, 1923). The material with soluble hydrochloride was neutralised with sodium bicarbonate and extracted with 100 parts of 75% alcohol. On concentrating the solution, orange micro-crystals were deposited in 40% yield, not melting at 350° and sparingly soluble in common solvents (Found: C, 68·6; H, 5·0; N, 10·3. $C_{13}H_9O_2N,2C_{13}H_{10}ON_2,3H_2O$ requires C, 68·3; H, 5·1; N, 10·2%). The substance is soluble in alkali and can be diazotised and coupled with β-naphthol (red), and hence may be designated a trihydrated *complex* of 2 : 8-dihydroxyacridine and 2-amino-8-hydroxyacridine.

m-*Diethylaminophenol.*—Only half the acid given under standard conditions was used, and heating at 155° was prolonged to 1¼ hours. The brilliant magenta-coloured melt was diluted with 50% aqueous zinc chloride solution and the crystals that separated were recrystallised from dilute hydrochloric acid. Yield, 55% of the zincichloride of 2 : 8-bisdiethylaminoxanthylium chloride (Pyronine B), which was compared with a commercial specimen.

m-*Aminodimethylaniline.*—This amine (15 g.) was added to a solution of zinc chloride (20 g.; 1·3 mols.) in glycerol (40 g.; 4 mols.) at 130° and hydrated oxalic acid (14 g.; 1 mol.) added. The temperature was raised to 155° (internal) during ½ hour and kept there for ¾ hour longer. The product was thinned with boiling water (90 ml.) and poured into excess of sodium hydroxide solution. The solid was filtered off, dissolved in dilute acid, and again precipitated with sodium hydroxide. It was dried, powdered, extracted with alcohol, and the extract cooled, depositing 0·62 g. of bis-(*m*-diethylamino)oxanilide, m. p. 198°. The filtrate, on concentration, gave crystals of the base of acridine-orange, m. p. 176°. Crystallisation from 9 parts of 65% alcohol gave solvated orange crystals which were dried at 120°; m. p. 181—182° [184—186° (corr.)]. This substance is less soluble in boiling water than is proflavine. Fluorescences in ultra-violet (Wood's) light: base (in alcohol), yellow-green becoming yellow when dilute; hydrochloride (in water), reddish-orange becoming yellow when dilute.

Oxalyl chloride was mixed at 0° with pyridine (5 mols.) followed by *m*-aminodimethylaniline (2 mols.). Dilution with water gave a 50% yield of *bis*-(m-*dimethylamino*)*oxanilide*, as cream coloured crystals from 300 parts of alcohol, m. p. 198° [203° (corr.)] (Found: C, 65·9; H, 7·0; N, 16·8. $C_{18}H_{22}O_2N_4$ requires C, 66·2; H, 6·8; N, 17·2%). This substance could not be acetylated, and was only slowly hydrolysed by boiling alkalis. Specimens prepared by the two methods did not depress one another's m. ps. The hydrochloride is white and insoluble in alcohol.

3-*Aminodiphenylamine.*—This was condensed with formic acid under the standard conditions, plus ½ hour at 175°. The product was boiled with water and collected. The crude, insoluble *hydrochloride* of 2 : 8-bis(phenylamino)acridine was extracted with 1000 parts of boiling alcohol, and the extract concentrated and then diluted with water. This was repeated several times giving scarlet micro-crystals, not melting at 365°. Soluble in propylene glycol, carbitol, and benzyl alcohol without temperature gradients. The solutions are orange and fluoresce orange in ultra-violet light (Found: C, 75·2; H, 5·3; N, 10·7. $C_{25}H_{19}N_3,HCl$ requires, C, 75·4; H, 5·1; N, 10·6%). The base is sparingly soluble in alcohol and other common solvents. Solutions are yellow and fluoresce green in ultra-violet light. No solvent in which it has any temperature gradient could be found.

2 : 6-*Tolylenediamine.*—This was condensed under the standard conditions, plus zinc chloride, the heating at 155° being prolonged to 5 hours. The method of working up the product has been described (Albert and Magrath, *J. Soc. Chem. Ind.*, 1945, **64**, 30). Yield, 57%. Varying the time of condensation gave 50% (1 hour), or 55% (3 or 7 hours). Varying the molecular proportion of hydrogen chloride (cf. graph for proflavine in Part II) gave 31% (0·55 mol.), 38% (0·85), 50% (1·00), 53% (1·30), and 45% (1·45). Raising the temperature to 175°, even for ½ hour, resinified the batch. 2 : 8-*Diamino*-1 : 9-*dimethylacridine* forms bright yellow solvated crystals from 2 parts of boiling acetone which, when dried in a vacuum and then at 120°, have m. p. 170° [173° (corr.)]. It is soluble in 18 parts of boiling benzene and 14 parts of boiling alcohol (poor gradients), almost insoluble in water and light petroleum. The alcoholic solution has a green fluorescence in daylight and a yellow in Wood's light (Found: C, 75·7; H, 6·4; N, 17·5. $C_{15}H_{15}N_3$ requires C, 75·9; H, 6·4; N, 17·7%). The orange-red hydrochloride is very soluble in water with green fluorescence. It gives a transient violet colour with nitrous acid and the ensuing yellow solution couples with β-naphthol (deep red).

The hydrochloride (2·74 g.) was suspended in acetic acid (50 ml.) and heated with acetic anhydride (2·5 g.; 5 equivs.) to 120° during ½ hour and maintained there for 1 hour longer, refrigerated, and the sparingly soluble hydrochloride of the acetyl derivative collected, washed with water, dried at 120°, and rubbed in a mortar with dilute ammonia until the scarlet colour changed to yellow. The base was filtered off, washed, and dried at 120°. After recrystallisation from 50% alcohol, in which it was more soluble than in absolute alcohol or water, yellow crystals were obtained, m. p. 259—262° (decomp., sealed), almost insoluble in benzene (Found: N, 14·95. $C_{17}H_{17}ON_3$ requires N, 15·05%). This

2-*amino*-8-*acetamido*-1 : 9-*dimethylacridine* is very soluble in water to an orange solution lacking fluorescence. The yellow diazonium solution couples with β-naphthol (dark red).

3 : 5-*Tolylenediamine*.—This (b. p. 184°/34 mm., prepared by the reduction of 3 : 5-dinitrotoluene with Raney nickel and hydrogen in alcohol) was condensed under the standard conditions plus an extra ½ hour at 175°. The reaction mixture was poured into dilute sodium hydroxide. The precipitate was filtered off, dissolved in dilute sulphuric acid, and the solution refrigerated. The sparingly soluble sulphate was recrystallised from dilute sulphuric acid, basified, and the 2 : 8-*diamino*-4 : 6-*dimethylacridine* recrystallised from 15 and then from 35 parts of alcohol. Yield, 20% of brownish-yellow crystals, m. p. 294—295° (sealed), slightly soluble in benzene with a temperature gradient. The solutions are yellow with a green fluorescence (Found: C, 75·4; H, 6·2; N, 17·5. $C_{15}H_{15}N_3$ requires C, 75·9; H, 6·4; N, 17·7%). The hydrochloride is more soluble in water than the isomeric acridine-yellow; the solutions are orange and develop a green fluorescence on dilution. Nitrous acid gives a violet solution which couples with β-naphthol (red).

3 : 5-*Diaminoanisole*.—This was prepared by the reduction (as above) of 3 : 5-dinitroanisole made from trinitrobenzene. Yield, 90% of a white, waxy solid which begins to melt at 66° to a viscous liquid, b. p. 198°/5·5 mm. 3 : 5-Diaminoanisole has not previously been obtained solid (Found: N, 20·45. Calc. for $C_7H_{10}ON_2$: N, 20·3%). When condensed under standard conditions it gave a brown resinous mixture, partly soluble in alkalis with a brilliant green fluorescence.

3 : 5-*Diaminobenzoic Acid Dihydrochloride*.—This (4·5 g.; 0·02 mol.), anhydrous sodium formate (2·04 g.; 0·03 mol.), glycerol (12 g.), and water (2 ml.) were heated to 155° during ½ hour, then to 185° in ½ hour and kept there for ½ hour longer. The melt was cooled, thinned with water (20 ml.), and refrigerated. The crystals of diaminoacridinedicarboxylic acid hydrochloride were dissolved in sodium carbonate solution, the solution filtered, and the filtrate acidified with acetic acid (yield, 65%). The *substance* was insoluble in all low-boiling solvents and in pyridine, nitrobenzene, carbitol, cellosolve, aniline, chlorobenzene, dioxan, phenol, phenylethyl alcohol, and methyl amyl ketone. It was purified by dissolving the mono-sodium salt in 67% acetone and fractionally precipitating it with acetic acid, which gave an orange, microcrystalline solid, not melting at 365° (Found, N, 14·2. $C_{15}H_{11}O_4N_3$ requires N, 14·1%). The di-sodium salt forms a gel with cold water. The acid could not be esterified with methanolic hydrogen chloride. It did not decarboxylate on heating to 365° nor on refluxing with copper in quinoline or diphenyl ether.

2 : 4-*Tolylenediamine*.—This was condensed as under standard conditions, plus ½ hour at 175° which materially improved the yield (72%). The latter was raised only to 75% by the use of zinc chloride. Oxalic acid (2 hours at 155°, plus zinc chloride) gave a 70% yield. The melt was diluted with twice its volume of water and precipitated with sodium hydroxide. The precipitate was dissolved in water (40 ml.) containing formic acid (1 ml., anhydrous) and ammonia was added until litmus was just blued. A small precipitate of a weak base was filtered off; this substance (3% yield, if a diacridyl ether) forms a very soluble hydrochloride and, if not removed, can prevent acridine-yellow base from crystallising from alcohol. The strong base was precipitated with sodium hydroxide and recrystallised from 180 parts of alcohol, giving yellow crystals of 2 : 8-diamino-3 : 7-dimethylacridine, m. p. 325° (sealed or open tube). The alcoholic solution has an intense green fluorescence (Found: C, 76·1; H, 6·4; N, 17·5. Calc. for $C_{15}H_{15}N_3$: C, 75·9; H, 6·4; N, 17·7%). It is soluble in 20 parts of N/4-lactic acid. The sparingly soluble hydrochloride gives an intense purple colour with nitrous acid which fades on standing for a short time and couples with β-naphthol (red).

2 : 4-*Diaminoanisole*.—This was prepared by suspending an equimolecular amount of 4-nitro-2-aminoanisole in alcohol and hydrogenating at atmospheric temperature and pressure in the presence of Raney nickel. The filtered solution was rapidly treated with the requisite amount of hydrochloric acid, the alcohol driven off, and the residue treated as in the standard reaction (plus ½ hour at 175° which doubled the yield). The diluted melt was made strongly alkaline with sodium hydroxide, boiled, cooled, and filtered. The precipitate was extracted with N/20-hydrochloric acid, and the filtered extract was adjusted with hydrochloric acid until 3% was present, and refrigerated. The hydrochloride was collected and basified, giving 2 : 8-*diamino*-3 : 7-*dimethoxyacridine*, which was purified by dissolution in 60 parts of alcohol and concentration to one third volume (supersaturation technique). Solvated hygroscopic yellow needles, m. p. 244° (sealed), were obtained in 20% yield based on the nitroanisidine. They were sparingly soluble in benzene, moderately in water with a temperature gradient, moderately in acetone with bluish fluorescence. The alcoholic solution is brown with an intense green fluoreseencc (Found, for material dried at 120° in air: C, 65·5; H, 5·7; N, 15·2. $C_{15}H_{15}O_2N_3,\frac{1}{2}H_2O$ requires C, 65·4; H, 5·7; N, 15·3%). The orange hydrochloride is sparingly soluble in water (intense green fluorescence) and is completely precipitated by chloride ions. It gives a red solution with nitrous acid which couples with β-naphthol (scarlet). The addition of zinc chloride to this condensation did not affect the yield. Heating at 200°, even for ½ hour, completely spoilt the condensation.

2 : 4-*Diaminophenetole*.—This was prepared from 2 : 4-dinitrophenetole similarly to the previous example and, without isolation, condensed and worked up in the same way. 2 : 8-*Diamino*-3 : 7-*diethoxyacridine* formed pale yellow crystals from 150 parts of benzene, m. p. 238° (not raised by further recrystallisation from benzene, alcohol, or pyridine). Yield (based on dinitrophenetole), 20%. The pale yellow solution in alcohol has an intense green fluorescence (Found: C, 68·7; H, 6·5; N, 15·8 (the nitrometer contained ethane). $C_{17}H_{19}O_2N_3$ requires C, 68·6; H, 6·5; N, 14·1%). This is evidently not the brown substance, m. p. 281°, obtained by the action of formic acid on 2 : 4-diaminophenetole in B.P. 248,182. The hydrochloride produces orange solutions in water with a green fluorescence, when very dilute, and foaming properties which persist on dilution. It is more soluble than the dimethoxy-analogue but is precipitated by N/2-hydrochloric acid. It gives no colour with nitrous acid and couples with β-naphthol (scarlet).

4-*Chloro*-1 : 3-*diaminobenzene*.—This was condensed as in the standard method using zinc chloride and prolonging the heating at 155° for 3 hours. Heating at 175° caused resinification; omission of zinc chloride severely lowered the yield. The melt was poured into N-sodium hydroxide and filtered. The precipitate was extracted with cold N-acetic acid, filtered from resinous material, and reprecipitated.

The precipitate was dissolved in boiling 0·5N-hydrochloric acid and chilled overnight. The hydrochloride was filtered off, heated with excess of ammonia solution, and dried at 120°. The 3 : 7-*dichloro*-2 : 8-*diaminoacridine* was recrystallised by extracting it with 150 parts of alcohol and concentration to 40 parts (supersaturation). It formed orange-yellow crystals (35% yield) which decomposed above 300° (sealed tube). It is only sparingly soluble in common solvents and the solutions have a green fluorescence (Found: C, 56·2; H, 3·6; N, 14·8. $C_{13}H_9N_3Cl_2$ requires C, 56·1; H, 3·3; N, 15·1%). The hydrochloride fluoresces green in dilute solution. It gives no colour with nitrous acid but couples with β-naphthol (scarlet).

The above reaction gave a by-product soluble in 0·5N- (but insoluble in 2N-) hydrochloric acid. The free base, which contains chlorine, was obtained as yellow crystals from dilute alcohol (Found: C, 54·5; H, 3·3; N, 14·6. $C_{26}H_{18}ON_6Cl_4$ requires C, 54·5; H, 3·2; N, 14·7%). This substance is apparently 3 : 7 : 3′ : 7′-*tetrachloro*-2 : 8 : 2′ : 8′-*tetra-amino*-5 : 10-*dihydrodiacridyl* 5 : 5′-*ether* and not an isomeride of 3 : 7-dichloroproflavine as was previously suggested (Albert, *J.*, 1939, 920). Neithe base nor salts fluoresce in solution. It diazotises and couples with β-naphthol (red).

2-*Dimethylamino*-p-*toluidine*.—This was prepared from pure dimethyl-*o*-toluidine and carefully fractionated. It was condensed under the standard conditions (plus ½ hour at 175°), cooled, diluted with water, and made alkaline with sodium hydroxide. The pasty precipitate was recrystallised from dilute alcohol and then from 10 parts of absolute alcohol. 2 : 8-*Bismethylamino*-3 : 7-*dimethylacridine* was obtained in 20% yield as yellow crystals, m. p. 308—309° (sealed), moderately soluble in acetone and sparingly in toluene but with good gradient. The alcoholic solutions fluoresce intense green (Found: C, 76·4; H, 7·2; N, 15·6. $C_{17}H_{19}N_3$ requires C, 76·9; H, 7·2; N, 15·8. 2 : 8-Bisdimethylamino-3 : 7-dimethylacridine, $C_{19}H_{23}N_3$, requires C, 77·8; H, 7·9; N, 14·3%). The hydrochloride is orange and readily precipitated by chloride ions. The solution in water has a green fluorescence when dilute. It could not be diazotised and coupled. No other pure product was isolated.

Non-symmetrical Condensations.—All the examples cited in D.R.-PP. 149,409, 149,410, 346,962, and 346,963 were attempted with the results stated in the Introduction, and no modification of the conditions produced non-symmetrical products. The following was more successful (D.R.-P. 161,699; Example 4). 2 : 4-Tolylenediamine dihydrochloride (1·95 g.; 0·01 mol.), diformyl-1 : 3-tolylenediamine (1·78 g.; 0·01 mol.), *m*-diethylaminophenol (1·67 g.; 0·01 mol.), and anhydrous glycerol (10 g.) were heated to 155° during ½ hour and kept there for 1½ hours. The melt was diluted with water (20 ml.) and treated with sodium hydroxide until Orange II paper was reddened, and the precipitate was collected, washed, and dissolved in N-acetic acid. The filtered solution was made 0·5N with hydrochloric acid and chilled overnight. The yellow precipitate, on basification, gave pure acridine-yellow base, m. p. and mixed m. p. 325° (yield, 25%). The filtrate was basified, and the solid was extracted with toluene, filtered from some red material, and concentrated until it crystallised. Further recrystallisation from a little acetone gave orange crystals of 2-*amino*-8-*diethylamino*-3-*methylacridine*, m. p. 216—217° (sealed) in 14% yield (Found: C, 77·2; H, 7·5; N, 15·0. $C_{18}H_{21}N_3$ requires, C, 77·4; H, 7·6; N, 15·0%). Identical results were obtained when this condensation was carried out on 1 : 3-tolylenediamine and *m*-diethylaminophenol under the standard conditions, the heating at 155° being prolonged to 1½ hours. The orange hydrochloride is soluble in hydrochloric acid of all concentrations and its solutions have only a slight fluorescence in daylight. With nitrous acid it gives an intense blue, stable solution that couples with β-naphthol (scarlet). These highly coloured (usually blue or violet) colours with nitrous acid are given by 2 : 8-diaminoacridine and several of its derivatives (see above) and also by 2 : 6- (but not by 2 : 7-, or 3 : 7-) diaminoacridine (Albert and Linnell, *J.*, 1936, 1614) and not by any of the monoaminoacridines. The present example and the next make it clear that only one *primary* amino-group is required for the production of the colour.

Attempt to produce 2-*Amino*-8-*dimethylamino*-3 : 7-*dimethylacridine* (D.R.-P. 292,848; Ex. 2).—2-Dimethylamino-*p*-toluidine dihydrochloride (2·33 g.; 0·01 mol.), 2-amino-4-formamidotoluene (1·5 g.; 0·01 mol.) and glycerol (8 g.) were heated to 155° during ½ hour, kept there for ½ hour, and kept at 175° for ½ hour. (On another occasion heating was continued for 6 hours at 185° causing greater decomposition.) The melt was diluted with 0·5N-hydrochloric acid and chilled; it then deposited crystals of pure acridine-yellow (m. p. and mixed m. p. of amine 325°) in 35% yield based on the 2-amino-4-formamidotoluene. The filtrate was basified and the precipitate taken up in N-acetic acid, filtered from weak bases, and basified. The precipitate was crystallised from 50% acetone and then from toluene. Yellow crystals of 2-*amino*-8-*methylamino*-3 : 7-*dimethylacridine*, m. p. 264° (sealed), very soluble in alcohol with intense green fluorescence, were obtained in 20% yield (Found: C, 76·3; H, 6·7; N, 16·95. $C_{16}H_{17}N_3$ requires C, 76·4; H, 6·8; N, 16·7%). The acetate is orange and very soluble in water. The dihydrochloride is soluble in 3N-hydrochloric acid from which it is partly precipitated as monohydrochloride on dilution to 0·5N; however, 0·1N-acid does not contain a sufficient concentration of chloride ion to precipitate the latter. Solutions of the salts fluoresce intensely green when dilute and give violet solutions with nitrous acid which couple with β-naphthol (red). No other pure product could be isolated. The same results were obtained (with unformylated amine) under the standard conditions plus ½ hour at 175°.

2-*Amino*-4-*formamidotoluene*.—2-Nitro-*p*-toluidine (15·0 g.; 0·1 mol.), formic acid (10 ml.), and toluene (50 ml.) were heated so that the vapours slowly distilled through a Widmer (spiral) column while the temperature of the bath was gradually raised to 170°. When no more liquid distilled below 105° (about 2 hours), the flask contents were poured into a dish, cooled, powdered, and dried at 120°. Yield, 17·75 g. (quantitative) of buff crystals of 2-*nitro*-4-*formamidotoluene*, m. p. 133—134°; not raised by recrystallisation from toluene, or from alcohol (3 parts) (Found: N, 15·4. $C_8H_8O_3N_2$ requires N, 15·55%). When this compound (8·9 g.) was suspended in alcohol (50 ml.) and hydrogenated with Raney nickel and hydrogen at atmospheric temperature and pressure, and the solution filtered, concentrated to 12 ml., and refrigerated, buff crystals of 2-*amino*-4-*formamidotoluene* were obtained in 85% yield, m. p. 112—113°, raised by repeated recrystallisation from toluene to 113—114° (Found: N, 18·8. $C_8H_{10}ON_2$ requires N, 18·7%). The only previous reference to these two substances is in D.R.-P. 138,839.

This work was supported by the University of Sydney and the National Health and Medical Research Council. The author is grateful to Professor J. C. Earl and Miss D. K. Large for their interest in this work, to Dr. G. Weiler, Mrs. L. Buckley, and Miss J. Fildes for the microanalyses, and to the Wellcome Foundation for providing secretarial and other assistance.

THE UNIVERSITY OF SYDNEY. [*Received, June 20th*, 1946.]

NOTES.

The Copper Sulphide-catalysed Dimerisation of iso*Butylene.* By A. WASSERMANN and W. T. WELLER.

IT has been shown that copper sulphide, activated by conversion of a part of its surface into copper sulphate, acts as a catalyst for the low-molecular polymerisation of *iso*butylene (Wassermann, B.P. 499,953). We have now found that in this reaction at least 40% of the starting material is converted into a mixture of the 2 : 2 : 4-trimethylpentenes, which are also obtained if *tert.*-butyl alcohol is treated with sulphuric acid (cf. Edgar, *Ind. Eng. Chem.*, 1927, **19**, 146).

*iso*Butylene was prepared from purified *tert.*-butyl alcohol (m. p. 25°) by a method similar to that indicated by Deanesly (U.S.P. 2,012,785); it was bubbled through water, dried with solid potassium hydroxide, and redistilled, a middle fraction boiling between − 7° and − 6° (761 mm.) being used. The catalyst was made by slowly adding 1·4 l. of 1M-sodium sulphide solution to 5 l. of 0·3M-cupric sulphate; the precipitate was filtered off (filter press), washed with water, spread in a thin layer on a tray, and dried for 24 hours at 80° in a stream of continuously renewed dry air at atmospheric pressure. 180 G. of catalyst were obtained, which contained 79—80% of cupric sulphide and 16—17% of cupric sulphate. 30 G. of this catalyst, 125 g. of *iso*butylene, and some nitrogen were introduced into a stainless-steel autoclave, which was placed for 100 hours in an oil-bath kept at 150° ± 0·5°, the pressure decreasing during this time from 30 to 26 atm. After being cooled to room temperature, the degased liquid product weighed 95 g.; 80 g. of this (*viz.*, 100 cm.³) boiled below 125°, and this fraction (I) was further investigated. It was left for 12 hours in contact with solid potassium hydroxide and then redistilled through a 10-inch reflux column. The fractions thus obtained are characterised by the data in lines 1—4 of Table I. The dimer (II), refered to in line 5, was an authentic mixture of the two 2 : 2 : 4-trimethylpentenes prepared according to Edgar (*loc. cit.*; cf. also Tongberg, Pickens, Fenske, and Whitmore, *J. Amer. Chem. Soc.*, 1932, **54**, 3706). The mixed m. p.'s listed in the last two lines were determined by using 50/50 mixtures. Both I and II consumed slightly more than 2 atoms of bromine per mol. of dimer.

TABLE I.

Dimer.	Fraction No.	Boiling range (760·5 mm.).	Vol. (cm.³).	M. p.	$n_D^{20°}$.	$d_{4°}^{20°}$.
I	1	<100°	16	− 97° ± 2°	1·4058	—
	2	100—101	44	− 98° ± 2°	1·4109	0·7184
	3	101—102	22	−104° ± 2°	1·4111	—
	4	>102	18	—	—	—
II	—	101·1—102·2	140	−104° ± 1°	1·4109	0·7180
I (Fraction 2) + II	—	—	10	− 99° ± 1°	—	—
I (Fraction 3) + II	—	—	10	−104° ± 1°	—	—

TABLE II.

	Boiling range (760·0 mm.).	% of initial vol.	M. p.*	$n_D^{20°}$.	$d_{4°}^{20°}$.
Hydrogenated dimer I	99—100°	86	−106° ± 1°	1·3918	0·6920
Authentic 2 : 2 : 4-trimethylpentane	99·4	—	−107°	1·3915	0·6918

* The mixed m. p. of these two specimens was −106°.

In order further to identify the dimer I, fractions 2 and 3 were catalytically hydrogenated by shaking, at room pressure and temperature, with carefully purified hydrogen and 5 g. of a platinum oxide catalyst prepared according to Adams and Shriner (*J. Amer. Chem. Soc.*, 1923, **45**, 2171). When 70% of the theoretically required volume of hydrogen had been consumed, the catalyst appeared to be poisoned, probably by traces of sulphur compounds in I; the theoretical amount of hydrogen was taken up when 9 g. of a fresh platinum catalyst, prepared according to Vavon (*Ann. Chim. Phys.*, 1914, **1**, 144), were added. The hydrogenated product was stable towards bromine; it was dried with calcium chloride and redistilled. The fractions thus obtained are characterised by the data in Table II, which contains for comparison data relating to authentic 2 : 2 : 4-trimethylpentane (Edgar, *loc. cit.*; Smith and Matheson, *J. Res. Nat. Bur. Stand.*, 1938, **20**, 641; Brooks, *ibid.*, **21**, 847).—DEPARTMENT OF CHEMICAL TECHNOLOGY, IMPERIAL COLLEGE, LONDON, S.W.7. [*Received, May 1st*, 1946.]

Improved Preparation of 4 : 4′-*Diaminobenzil and* 2 : 2′-*Dihydroxybenzil.* By HERBERT L. GEE and JOHN HARLEY-MASON.

THE preparation and bacteriostatic properties of 4 : 4′-diaminobenzil (I) were described by Kuhn, Möller, and Wendt (*Ber.*, 1943, **76**, 405), the compound being obtained by reduction of 4 : 4′-dinitrobenzil by hydrogenation or by ferrous sulphate and ammonia. Precise details of the mode of reduction are not given, the yield is not stated, and 4 : 4′-diaminobenzoin is obtained as a by-product.

We have found that (I) can most readily be prepared from *p*-aminobenzaldehyde, which, after acetylation, can be converted into 4 : 4′-*diacetamidobenzoin* by potassium cyanide in alcohol. The benzoin was oxidised almost quantitatively to the benzil by copper sulphate and pyridine, and hydrolysis with hydrochloric acid then yielded (I). The yield of the benzoin was rather poor (*ca.* 30%), but the ready availability of the starting material, prepared by treatment of *p*-nitrotoluene with sodium polysulphide and alkali (Beard and Hodgson, *J.*, 1944, 4), makes this fact of little consequence.

p-Aminobenzaldehyde and 4-acetamido-2-methoxybenzaldehyde both failed to undergo benzoin condensation with boiling alcoholic potassium cyanide.

2 : 2′-Dihydroxybenzil was prepared by Kuhn, Birkhofer, and Möller (*Ber.*, 1943, **76**, 900) by demethylation of 2 : 2′-dimethoxybenzil with aluminium chloride in nitrobenzene. This procedure is not applicable to the preparation of the compound in quantity, and we have found that quantitative demethylation can readily be accomplished by heating the dimethoxy-compound with pyridine hydrochloride.

4 : 4′-*Diacetamidobenzoin.*—Crude *p*-aminobenzaldehyde (from 40 g. of *p*-nitrotoluene) was stirred with acetic anhydride (50 c.c.). When the exothermic reaction was complete, the mixture was poured into water and the *p*-acetamidobenzaldehyde collected and recrystallised twice from aqueous alcohol. *p*-Acetamidobenzaldehyde (10 g.), alcohol (30 c.c.), and potassium cyanide (1 g.) were refluxed for 2 hours. The mixture was diluted with water, and next day the 4 : 4′-diacetamidobenzoin (2·8 g.) which had separated was collected and recrystallised from acetic acid; m. p. 244—246° (Found : C, 66·2; H, 5·8. $C_{18}H_{18}O_4N_2$ requires C, 66·5; H, 5·5%).

4 : 4′-*Diaminobenzil.*—Copper sulphate (3 g.), pyridine (5 c.c.), and water (2 c.c.) were heated until a homogeneous solution was obtained. 4 : 4′-Diacetamidobenzoin (2 g.) was added and the mixture was kept for 2 hours at 100° with occasional stirring and then poured into water. The product (1·8 g.) was filtered off and recrystallised from acetic acid. The diacetyl derivative was boiled with concentrated hydrochloric acid (10 c.c.) for 0·5 hour. On cooling, the dihydrochloride which had separated was collected and dissolved in water, and the 4 : 4′-diaminobenzil (1·2 g.) precipitated with ammonia. After being recrystallised from alcohol it had m. p. 169°.

2 : 2′-*Dihydroxybenzil.*—2 : 2′-Dimethoxybenzil (20 g.) and pyridine hydrochloride (40 g.) we mixed and heated at 180° for 2 hours. After cooling, water was added, and the crude product collected, dissolved in 10% sodium hydroxide solution, filtered from impurities, and precipitated with dilute acid. After recrystallisation from acetic acid it had m. p. 154—155°. Yield, 16·5 g.

We are indebted to the Director General of Scientific Research (Defence), Ministry of Supply, for permission to publish this note, and to Mr. J. H. R. Slade for experimental assistance.—UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 21st,* 1946.]

Discussion on "Some Aspects of the Chemistry of Macromolecules."

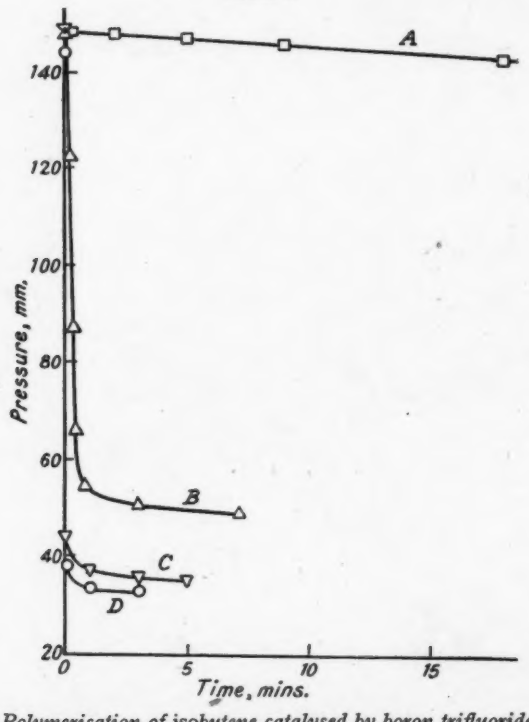
HELD AT THE INSTITUTION OF MECHANICAL ENGINEERS, LONDON, ON APRIL 4TH, 1946.

1. *Polymerisation of* iso*Butene by Friedel–Crafts Catalysts.*

By ALWYN G. EVANS and M. POLANYI.

AN investigation of the polymerisation of *iso*butene by boron trifluoride, and the study of related reactions, pursued over a number of years, have brought evidence that the presence of a trace of some third component is essential in order that the process may take place at an appreciable rate (A. G. Evans, Holden, Plesch, Polanyi, Skinner, and Weinberger, *Nature*, 1946, **157**, 102). In the case of titanic chloride acting on *iso*butene this "activator" has been now identified as water.*

FIG. 1.



Polymerisation of isobutene *catalysed by boron trifluoride.*
(The reaction is followed by the fall in the isobutene *pressure.)*

Curve A: 100 *Mm. of distilled* isobutene + 50 *mm. of* BF_3.
Curve B: 100 *Mm. of undistilled* isobutene + 47 *mm. of* BF_3.
Curve C: 90 *Mm. of distilled* isobutene + 11·5 *mm. of residue vapour* + 47 *mm. of* BF_3.
Curve D: 105 *Mm. of distilled* isobutene + 5 *mm. of* tert.-*butyl alcohol* + 33 *mm. of* BF_3.

We can now report another instance of this kind from experiments carried out in collaboration with G. W. Meadows. The normal experience, which we have confirmed by numerous experiments, is that *iso*butene, whether as pure liquid or in solution, reacts instantaneously (in the absence of inhibitors) on the passage of boron trifluoride through it at low temperatures. We find that *iso*butene in the gas phase can be mixed with the trifluoride without showing any fast reaction.† *iso*Butene, distilled in a vacuum from — 80° to liquid air, was mixed at pressures of 50—100 mm. with boron trifluoride at pressures of about 50 mm., and only a slow fall in pressure was observed. An example is shown in curve *A* of Fig. 1.

Similar mixtures reacted instantaneously when certain impurities were present. This was

* See subsequent paper.
† Such mixtures always reacted on condensation in liquid air.

the case (1) for undistilled *iso*butene technically prepared from *tert.*-butanol (reported 99% pure) (Curve *B*), (2) for *iso*butene distilled as before to which the vapour from the residue of distillation was added in a fraction of 1—10% (Curve *C*), (3) for *iso*butene distilled as before to which 5% of *tert.*-butanol was added (Curve *D*). We observed that in the cases (2) and (3) the trifluoride was consumed in quantities approximately equivalent to the mols. of activator added.

We conclude that (*a*) the trifluoride does not form a stable complex with *iso*butene; (*b*) no rapid reaction takes place in the gas phase (either at ordinary or at reduced temperatures down to about − 60°) unless a third substance is present; (*c*) in the presence of *tert.*-butanol vapour instantaneous reaction occurs, which (by the formation of a mist) can be seen to proceed in the gas phase—it is still uncertain whether this is responsible for the reaction of the undistilled *iso*butene as described above.*

In view of these points it seems necessary to conclude (in deviation from our previous assumption, *Nature*, **1943**, **152**, 738) that the following carbonium mechanism plays some part in these polymerisations.

$$BF_3 + YH \longrightarrow F_3BYH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$F_3BYH + CH_2{=}C(CH_3)_2 \longrightarrow F_3BY^{\ominus} + CH_3{-}C^{\oplus}(CH_3)_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$CH_3{-}C^{\oplus}(CH_3)_2 + CH_2{=}C(CH_3)_2 \longrightarrow CH_3{-}C(CH_3)_2{-}CH_2{-}C^{\oplus}(CH_3)_2 \text{ etc.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Steps similar to (2) and (3) have been discussed by Whitmore (*Ind. Eng. Chem.*, **1934**, **26**, 94), Hunter and Yohe (*J. Amer. Chem. Soc.*, **1933**, **55**, 1248), Brunner and Farmer (*J.*, 1937, 1039), and Price (*Ann. N.Y. Acad. Sci.*, **1943**, **44**, 368). It is therefore important to estimate the basicities of various olefins, in terms of "proton affinities" and "carbonium-ion affinities" as defined in the following equations:

$$H^{\oplus} + M \longrightarrow HM^{\oplus} + P \quad \text{(proton affinity)}$$
$$M_n^{\oplus} + M \longrightarrow M_{n+1}^{\oplus} + C \quad \text{(carbonium-ion affinity)}$$

The proton affinities of olefins may be determined by the following steps, the proton in this example being added to carbon 1.

$$R_1R_2C{=}CH_2 + H^{\oplus} + e \longrightarrow R_1R_2\dot{C}{-}CH_3 + i - \beta + D$$

$$R_1R_2\dot{C}{-}CH_3 \longrightarrow R_1R_2C^{\oplus}{-}CH_3 + e - I$$

$$R_1R_2C{=}CH_2 + H^{\oplus} \longrightarrow R_1R_2C^{\oplus}{-}CH_3 + P$$

Proton affinity: $P = i - \beta + D - I$, where $i =$ ionisation potential of hydrogen (taken as 312 kcals.), $\beta =$ energy of second half of double bond, $D =$ carbon–hydrogen bond strength, $I =$ ionisation potential of radical formed by addition of hydrogen atom to olefin.

For any non-symmetrical olefin the proton affinity for addition to carbon 1 will be different from that for addition to carbon 2. In Table I we give the calculated proton affinities for ethylene, propylene, and *iso*butene.

TABLE I.

Proton affinities and atom affinities of olefins.

Olefin.	β.	D_1.	D_2.	I_1.	I_2.	P_1.	P_2.	A_1.	A_2.
$CH_2{:}CH_2$	57·5	97·5	97·5	200	200	152	152	40	40
$CH_2{:}CHMe$	52·5	95	89	179	180	175·5	168·5	42·5	36·5
$CH_2{:}CMe_2$	52·0	94	86	165	178	189	168	42	34

The values of β and D (D_1 and D_2 for additions to carbon atoms 1 and 2, respectively) are taken from the revised table of bond energies of Baughan and Polanyi quoted by Butler and Polanyi (*Trans. Faraday Soc.*, **1943**, **39**, 19); I_1 and I_2 are the ionisation potentials of the radicals

* *Note Added in Proof.*—This point has since been cleared up; traces of water have been found to be responsible for this reaction (A. G. Evans, Meadows, and Polanyi, *Nature*, **1946**, **158**, 94).

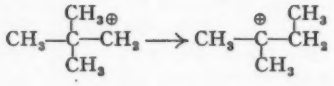
which are formed by the addition of a hydrogen atom to the olefin at carbon 1 and carbon 2, respectively. The value of I for the ethyl radical has been determined by electron-impact experiments (Hipple and Stevenson, *Physical Rev.*, **1943**, **63**, 121). We have estimated the other values of I from the results of electron-impact experiments (*idem*, *J. Amer. Chem. Soc.*, **1942**, **64**, 1590, 2766, 2769), and these values have been critically discussed elsewhere (A. G. Evans, *Trans. Faraday Soc.*, in the press).

The carbonium ion affinities (C_1 and C_2 corresponding to P_1 and P_2) will follow the same sequence as the proton affinities. The results of more detailed calculations are given later.

It is seen that P_1 (and therefore C_1) increases markedly from ethylene to *iso*butene. This would account for the increase in the ease of polymerisation as the olefin changes from ethylene, which is unaffected by these catalysts, to *iso*butene, which is so highly reactive.

It is also seen from Table I that for *iso*butene P_1 is much greater than P_2. This means that a proton will add to the *iso*butene double bond more readily at the CH_2 than at the CMe_2 end. Thus, if the addition of HX to a double bond involves an initial proton attack, then the H will add on to the carbon with the greater number of hydrogen atoms on it. We may thus interpret Markownifkoff's rule in terms of bond strengths and ionisation potentials.

The difference between C_1 and C_2 may also be expressed as follows. A carbonium ion will tend to rearrange itself so that the carbonium carbon will carry the greatest number of alkyl groups. This effect is found to operate for the *neo*pentyl derivatives in which all reactions of the carbonium-ion type yield exclusively products rearranged as follows in accordance with this prediction (Whitmore and Fleming, *J.*, 1934, 1269; Whitmore and Rothrock, *J. Amer. Chem. Soc.*, 1932, **54**, 3431):



From the above discussion, therefore, we should expect the carbonium ion produced in the initiation reaction (2) to be the tertiary ion $CH_3{\cdot}\overset{\oplus}{C}Me_2$.

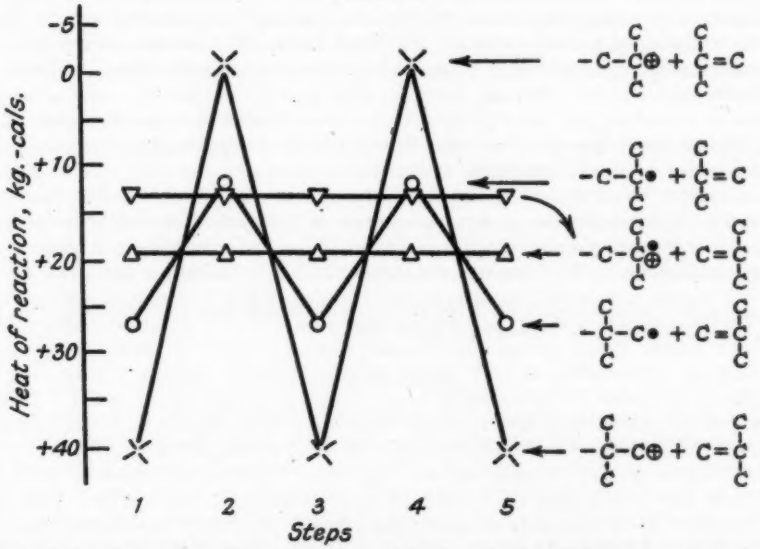
In the propagation reaction (3) the olefin monomer will be attacked by the carbonium carbon of the growing polymer chain. By analogy with the initiation reaction we might expect that at each step in the propagation the attack of the carbonium ion on the monomer is at its tail end, so that at the end of the growing polymer chain there is always a head $\cdot CH_2{\cdot}\overset{\oplus}{C}Me_2$ and not a tail $\cdot CMe_2{\cdot}\overset{\oplus}{C}H_2$. This would result in a head-to-tail propagation process, and would exclude the tail-to-head, and the head-to-head, tail-to-tail types of propagation.

We can give a more detailed calculation of the propagation process as follows. For the head-to-tail addition we have previously calculated the heat of reaction as 21·4 kcals. (*loc. cit.*). Using the more recent heats of formation obtained by Prosen and Rossini (*J. Res. Nat. Bur. Stand.*, 1945, **34**, 263), we have recalculated this value for the head-to-tail step as 19·5 kcals. From the data given by Baughan and Polanyi (*loc. cit.*) and by Prosen and Rossini (*loc. cit.*), together with the ionisation potentials of the *tert.*- and *iso*-butyl radicals given in Table I, we have calculated the tail-to-tail addition step as about 40 kcals. exothermic, and the head-to-head step as slightly endothermic. Thus, of the three possible steps for the carbonium-ion mechanism, the tail-to-tail addition is most probable, the head-to-tail addition is still quite probable, but the head-to-head addition is very improbable. Since the tail-to-tail addition can only occur in chain propagation if the head-to-head addition is also involved, this discussion indicates that for a carbonium-ion mechanism, however the chain starts, it will always proceed with the head as the positive end $\cdot CH_2{\cdot}\overset{\oplus}{C}Me_2$, and this will lead to the head-to-tail type of addition with a constant heat of reaction of 19·5 kcals. at each step. This is shown in Fig. 2. In this figure we have also included the heats of reaction for the consecutive steps of the head-to-head, tail-to-tail mechanism, which alternate between slight endothermicity and compensating strong exothermicity.

It is found that poly*iso*butene has a head-to-tail structure (Thomas, Sparks, Frolich, Otto, and Mueller-Conradi, *J. Amer. Chem. Soc.*, 1940, **62**, 276; Fuller, Frosch, and Pape, *ibid.*, p. 1905) in accordance with what our previous considerations have led us to expect. This is the more remarkable since in the head-to-tail structure of a 1 : 1-disubstituted ethylene like *iso*butene there is a steric hindrance between the substituent groups of successive monomer units, which would be absent, or very much less, in the head-to-head, tail-to-tail structure

(A. G. Evans and Polanyi, *loc. cit.*; A. G. Evans, *Trans. Faraday Soc.*, 1945, **41**, 273). A measure of this steric effect is given by the difference between the experimental value for the heat of polymerisation of *iso*butene, 12·8 kcals. (A. G. Evans and Polanyi, *loc. cit.*), and the value of 19·5 kcals. calculated above for the unstrained molecule. Yet the head-to-tail mechanism remains the only one possible, since the formation of the unstrained head-to-head, tail-to-tail structure is prevented by the endothermicity of the head-to-head step.

FIG. 2.



Heats of reaction for the steps involved in different types of propagation mechanisms.

△ *Head-to-tail radical or carbonium mechanism, when no steric hindrance is present.*
▽ *Head-to-tail radical or carbonium mechanism when steric hindrance is present.*
⊙ *Head-to-head, tail-to-tail radical mechanism.*
× *Head-to-head, tail-to-tail carbonium mechanism.*

Radical Mechanism.—In order to consider the radical mechanism of polymerisation, the "atom affinities" of the olefins are needed. These may be determined by the following step. (In the example given, the hydrogen atom is added to carbon 1.)

$$\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!C{=}CH_2 + \dot{H} \longrightarrow \begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!\dot{C}{-}CH_3 - \beta + D.$$

Atom affinity : $A = D - \beta$.

The atom affinities calculated in this way are given in Table I : A_1 and A_2 are the heats of addition of a hydrogen atom to carbon 1 and carbon 2, respectively. It is seen that, in contrast to the proton affinity of the olefin P_1, there is no marked increase in A_1 with change from ethylene to *iso*butene. Further, although for *iso*butene A_1 is greater than A_2, the difference is not so marked as the corresponding difference between P_1 and P_2. The alkyl radical affinities of the olefins vary in the same direction. We should thus expect that, for the radical mechanism, the heats of reaction of the head-to-head step and of the tail-to-tail step will not be as widely divergent from the heat of reaction of the head-to-tail step as is the case for the carbonium-ion mechanism.

We have made more detailed calculations of the heats of reaction of these steps for the radical mechanism, using the data of Baughan and Polanyi and of Prosen and Rossini (*locc. cit.*). We find that the tail-to-tail step will be exothermic by about 27 kcals., and the head-to-head step will be exothermic by about 12 kcals. The head-to-tail step, of course, would be exothermic by 19·5 kcals., but because of steric hindrance it is actually 12·8 kcals. exothermic. Thus, although in the absence of steric hindrance the radical mechanism would result in the head-to-tail type of addition, the presence of steric hindrance in this addition reduces its exothermicity and brings it close to that of the head-to-head step. This makes the head-to-head, tail-to-tail type

of addition possible as well as the head-to-tail type (see Fig. 2). In this case we should expect the chain to consist of a more or less random arrangement of linkages, and to result, therefore, in a non-crystalline polymer. It is interesting in this connection, that methyl methacrylate, sharing with *iso*butene the steric properties of a 1 : 1-disubstituted ethylene but polymerising by a radical mechanism, gives a non-crystalline polymer, whereas poly*iso*butene, on the other hand, is crystalline.

Activation Energies.—The above considerations have dealt with the heats of reaction of the various steps, whereas the critical factors involved will be their energies of activation. But there is no activation energy in the carbonium-ion propagation mechanism, for the energy of approach of a carbonium ion to a system of closed shells will vary monotonously, and so this reaction involves no energy barrier. All exothermic reactions of this kind will be instantaneous at all temperatures.

The heats of reaction will also govern the course of reaction in the case of the radical mechanism, for we may expect a decrease in activation energy whenever there is an increase in the exothermicity of a reaction step.

We can see also that the carbonium mechanism offers a possibility for the occurrence of polymerisation at the lowest temperatures, whereas a free-radical process would be inevitably slowed down by extreme cold.

Some suggestions about the termination mechanism are contained in the next paper.

The authors wish to acknowledge the stimulus and help which they have enjoyed from the Research Laboratories, I.C.I., Billingham, throughout their work.

Discussion.

MR. H. S. LILLEY (communicated) : In collaboration with Mr. G. L. Foster, I have recently been studying the polymerisation of styrene in the presence of phenols, using the electrophilic borofluoroacetic acid complex as catalyst. We have observed variable induction periods and reaction rates in successive duplicate runs, such as appear to have been noted by Professor Polanyi in the dimerisation of 2 : 2 : 4-trimethylpentene with boron trifluoride. We have, in general, attributed the effects we have noted to variable traces of water, these being difficult to control, and we have formed various (unproved) views as to the mode of action of water in this case. We are very interested therefore in Polanyi's work on the $TiCl_4$–H_2O–*iso*butene system, where water shows a pronounced catalytic effect, attributed by Polanyi to a hydrate of titanic chloride and its ions. It seems, however, possible that the halide might be hydrolysed by water with formation of hydrogen chloride. Although Polanyi shows that this acid is of null effect in his case, it is known that in the not dissimilar system styrene–stannic chloride, hydrogen chloride has a marked effect, as was shown by Williams (*J.*, 1938, 1046; 1940, 775, etc.). In this case hydrogen chloride acts as a temporary inhibitor of polymerisation and markedly reduces average molecular weight, besides introducing a side reaction of hydrochlorination. It is not *prima facie* easy to reconcile the data of Polanyi and of Williams. Many explanations can, of course, be mooted, such as difference in experimental conditions of temperature and phase, relative stability against hydrolysis of the covalent halides concerned, the degree of dryness achieved by Williams, etc.

MR. L. B. MORGAN (communicated) : The boron trifluoride-catalysed polymerisation of *iso*butene at low temperatures shows some unusual features which have hitherto been difficult to explain. Attention has already been directed to some of these in the similar reaction, the dimerisation of di*iso*butene by boron trifluoride by Polanyi *et al.* (*Nature*, 1946, **57**, 102). The polymerisation does not commence unless the concentration of trifluoride is above a certain threshold value; under some conditions the polymerisation does not occur if the BF_3 is added to the system slowly, and often the polymerisation does not proceed to completion although monomer and BF_3 are present together. It would appear from this that BF_3 is not, itself, the initiating catalyst, and the simplest kinetic scheme that will explain the phenomena is one involving a two-stage reaction of BF_3 with an impurity, the first reaction forming the true initiating entity and the second reaction destroying it, *i.e.*, a similar reaction form to that of reduction activation with ferrous ion and hydrogen peroxide or persulphate and thiosulphate. The likely impurities are water and butanol. If the operating impurity is water, the two consecutive reactions might be the formation, first, of the monohydrate followed by an ionisation with the second molecule of water forming oxonium ion, the active catalyst being the intermediate monohydrate or possibly a proton arising from its dissociation. If it is assumed that these reactions occur immediately the BF_3 is added to the system and before the polymerisation,

the threshold concentrations and the effect of rate of addition are readily explicable. With a carbonium-ion propagation mechanism and a termination involving reaction with anion, as proposed by Professor Polanyi, it is necessary to postulate an initiation independent of monomer concentration to explain the approximate unimolecular dependence of the polymerisation on monomer concentration and the fact that polymerisation ceases before all the monomer has been polymerised, and this suggests that the monohydrate ionises unimolecularly to give a proton which immediately initiates a polymerisation chain. This suggested initiating mechanism will not be general for all Friedel–Crafts initiated polymerisations. In the case of styrene, which is more readily initiated, the polymerisation is termolecular with respect to the monomer concentration, and Price (*Ann. N.Y. Acad. Sci.*, **1943**, **44**, 368) has suggested that the initiation here can be achieved more simply by a bimolecular reaction between monomer and monomer–catalyst complex, the association of the catalyst and the monomer being sufficient in this instance to form an incipient carbonium ion.

*iso*Butene will not polymerise under those polymerisation conditions which are believed to result in free-radical propagation, such as reduction activation, and the inference is that the chemical driving force in the free-radical propagation step is lower than in the carbonium-ion propagation step and is insufficient to overcome the strain energy required to pack the two methyl groups into the polymer chain. Although *iso*butene cannot be induced to polymerise by itself by free-radical initiators, it will interpolymerise with other vinyl monomers such as acrylonitrile and the possibility is that under these conditions the strain energy involved in the packing of the pendant groups into the interpolymer chains is much lower. An interesting case is the interpolymerisation of *iso*butene with fumaric or maleic esters under the influence of free-radical initiators: neither will polymerise alone, but in admixture the interpolymer is readily formed. There are several examples of interpolymerisation where it would appear that the interpolymerisation propagation step is faster than the propagation step of either component alone, and no stisfactory explanation has yet been advanced to explain this. One possibility is that there is association between pairs of the monomers and the interpolymerisation propagation step consists of additions of these associations as such to the growing polymer chain. Another possibility which is worth considering is that the strain energies of packing the pendant groupings into the polymer chain are less for the interpolymerisation than for the polymerisations of the individual monomers alone.

DR. A. G. EVANS, PROF. POLANYI, AND DR. SKINNER (communicated): In reply to H. S. Lilley and L. B. Morgan, we feel that the mechanism of Friedel–Crafts polymerisation has proved to be so complex that the present state of observations does not enable us to generalise much further. We would prefer therefore not to pursue the matter before we get more experiments done.

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2. *The Low-temperature Polymerisation of* iso*Butene by Friedel–Crafts Catalysts.*

By P. H. PLESCH, M. POLANYI, and H. A. SKINNER.

A COMPARATIVE study of the catalytic efficiency of several halides of the Friedel–Crafts type in promoting the polymerisation of *iso*butene at low temperatures was undertaken in these laboratories by Fairbrother and Seymour * in 1941—1942 (Seymour, Thesis, Manchester, 1943), who found that the power of catalytic activity decreases over a very wide range down the series BF_3, $AlBr_3$, $TiCl_4$, $TiBr_4$, BCl_3, BBr_3 and $SnCl_4$. Under comparable experimental conditions, the polymerisation of *iso*butene is completed within a period of seconds with BF_3, and hardly extends to a few minutes with $AlBr_3$, whereas reaction times of hours are found when we apply $TiCl_4$, and periods of days are required with the weakest of these catalysts ($SnCl_4$). The marked gradations in the activity of various catalysts, assessed in terms of reaction time and percentage yield of polymer formed, are summarised in Table I. Attention should be called to the fall in the polymer molecular weight with falling activity of the catalyst (clearly shown in the final column of Table I), which is discussed later in this paper.

An important feature of all these reactions, whether catalysed by BF_3, $AlBr_3$, or $TiCl_4$ and other catalysts of this series is the lack of reproducibility in the detailed course of the reaction. Even though in our own experiments we have tried to make the experimental conditions much more rigorous than those used by Fairbrother and Seymour, this characteristic of the reaction remained.

* The authors are indebted to Dr. F. Fairbrother and Mrs. E. L. Seymour for permission to quote results from their work.

TABLE I.

Catalytic activity of Friedel–Crafts catalysts (from Fairbrother and Seymour).

Catalyst, and %.	Starting temp. −78°. *iso*Butene, %.	Reaction time.	Yield of polymer, %.	Mol. wt. × 10^{-3}.
BF_3, 0·05	10	Seconds	100	120—150
$AlBr_3$, 0·05	20	1—5 Mins.	70—90	120—150
$TiCl_4$, 0·12—0·25	30	20—70 Mins.	35—50	100—130
$TiBr_4$, 1·0—1·5	30—50	12—18 Hrs.	30—50	70—90
BCl_3, 0·9—1·5	40—50	,,	0·5—1·5	30—50
BBr_3, 0·6—1·0	50	,,	0·5—1·5	20—30
$SnCl_4$, 1·5—2·5	50	17—50 Hrs.	10—18	12—25

The gradation is illustrated once more in Table II, which gives the threshold concentrations of the catalyst and monomer, below which polymerisation could not be observed.

TABLE II.

Threshold concentrations for polymerisation (from Fairbrother and Seymour).

Catalyst.		$AlBr_3$.	$TiCl_4$.	$TiBr_4$.	BCl_3.	$SnCl_4$.
Composition of reaction mixture	*iso*Butene, %	1·0	7·0	20	20	10
	Catalyst, %	0·01	0·12	0·50	0·8	1·0

Our investigations have so far been confined to the polymerisation by titanic chloride as catalyst, for this reaction proceeds at an easily measurable rate which can be conveniently followed by observing the rate of increase in temperature of the reaction mixture contained in a Dewar vessel. Fairbrother and Seymour conducted their experiments on titanic chloride in a similar manner, but used as reaction vessel a large test-tube cooled externally by immersion in a suitable cooling bath. They found that for reactions started in the temperature range — 60° to — 80°, no observable rise in temperature followed the addition of the chloride to the reaction mixture for a period of 10 minutes or more. A different behaviour was observed at lower starting temperatures (— 80° to — 120°). In this lower range the reactions started instantly on the mixing of the reagents. This increased activity at temperatures below — 80° was stated to be general for the reactions catalysed by the weaker catalysts listed in Table I.

Polymerisation by Titanic Chloride.—Preliminary experiments. In our preliminary experiments, the mixture of hexane and *iso*butene (80 : 20 by vol.) contained in a large test-tube was precooled to the required starting temperature (normally *ca.* — 80°) by immersion in a low-temperature bath, and then poured rapidly into the Dewar reaction vessel. Sufficient catalyst solution to give 0·5% of $TiCl_4$ in the mixture was added from a burette to start the reaction, the progress of which was followed by measurement of the temperature of the reacting mixture with a pentane thermometer at minute intervals.

Fifty-five experiments, in which the starting temperatures varied between — 30° and — 120° were completed with this procedure. The main points emerging from these observations were as follows:

(1) At starting temperatures above — 90° (approx.) the addition of catalyst produced only a small immediate temperature rise, followed, after a variable and irreproducible induction period, by a reaction of autocatalytic type, *i.e.*, having an S-shaped time–temperature curve [see Fig. 1(*A*)]. This is approximately the same result as observed by Fairbrother and Seymour at these temperatures. Below — 90°, the addition of catalyst produced an immediate fast reaction which did not go to completion, but the extent of which increased with reduction in the starting temperature. After this initial activity, the reaction slowed down and remained quiescent for a period, following which a second reaction set in of the same autocatalytic type as those observed at higher starting temperatures [see Fig. 1(*B*)]. Curve *B* shows that in the interval of quiescence between the first and the second stage of the reaction, the temperature fell by a few degrees: this fall cannot be attributed to the external cooling, and its true nature is not yet understood.

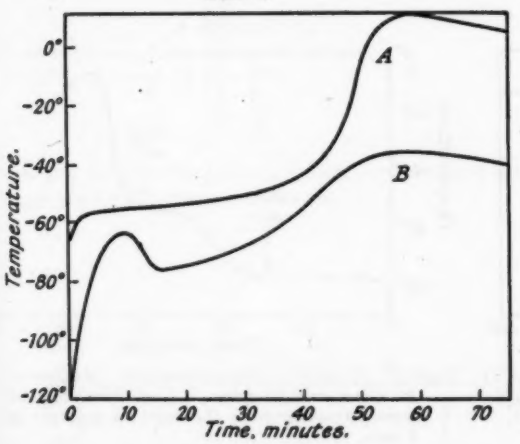
(2) The molecular weight of the polymers increased as the starting temperature of the reaction was reduced.

(3) The polymer yields in all the reactions we carried out indicated that the reactions had gone to completion or nearly so. This is at variance with some of the results of Fairbrother and

Seymour, who frequently obtained low yields, especially at low starting temperatures. This difference may be due to the more rigorous adiabatic conditions used in our experiments.

Later experiments : The effect of moist air. At this stage some alterations in the experimental technique were introduced, for apart from the cumbersome method used to precool the reactants, the earlier procedure allowed an uncontrolled access of laboratory air to the reaction mixture. The modified apparatus is shown diagrammatically in Fig. 2. The reaction vessel *R* is a double-walled "Pyrex" container, with a side arm cone-joint *C* connecting *R* to a high-vacuum pumping system; *R* is closed by a rubber stopper *S*, through which pass a mercury-sealed stirrer, pentane thermometer, and various inlet and exit tubes. Measured quantities of hexane and titanic chloride (purified by standard methods from the commercial products, and stored under dry air in sealed glass containers) were run into *R* from burettes, the transference of the liquids being effected by pressure-blowing with dry air or nitrogen. The *iso*butene (supplied by I.C.I., Billingham, and stated to be over 99% pure) was run into the reaction vessel from a graduated "Pyrex" trap. The cooling of the hexane–*iso*butene mixtures (20% *iso*butene by volume) was

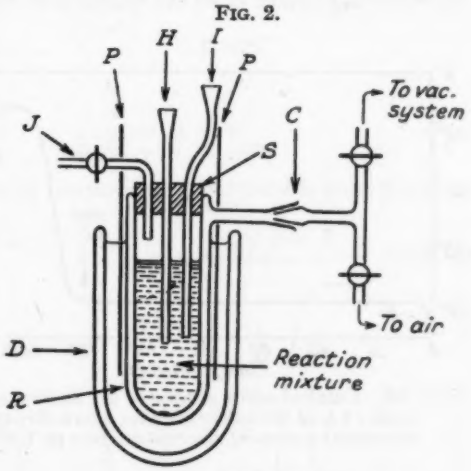
FIG. 1.



(A) *Expt.* 40.
(B) *Expt.* 23.

In both experiments 0·5% *of catalyst was added to* 20% iso*butene in hexane at time* = 0.

FIG. 2.



The reaction vessel.

R = *Reaction vessel, 20 cm. long, 5 cm. diameter.* C = B.14 *cone joint to vacuum system.* S = *Rubber stopper carrying pentane thermometer and mercury seal stirrer (not shown), and hexane and catalyst inlet* H, iso*butene inlet* I, *and gas exit* J. P = *Lead collar.* D = *Dewar vessel.*

performed in the vessel *R*, by immersing it in the liquid-air bath *D*. When the desired low temperature had been attained in *R*, the annular space between the walls of the reaction vessel was evacuated *via* the high-vacuum system, and *R* thereby temporarily converted into a Dewar vessel. Catalyst solution sufficient to give ½% $TiCl_4$ in the reaction mixture was then run into *R*, and the reaction carried out under adiabatic conditions and followed as previously in terms of the temperature changes. Improved thermal stability within the reaction vessel was attained by immersing the body of the Dewar flask in a liquid-air bath, and fitting a lead collar round its neck. With this arrangement there was very little leakage of heat into the reaction vessel from outside, and the mixture at − 80° could be kept at this temperature (± 1°) for long periods.

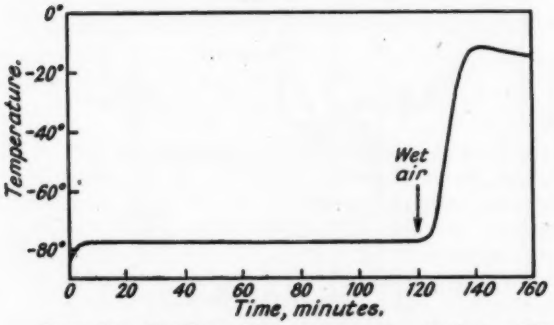
Using the modified apparatus, we were surprised to find that the addition of catalyst to the monomer solution at − 80° failed to induce polymerisation. This observation was confirmed several times. That this inability to enter into reaction was due in some way to the absence of laboratory air from the reaction vessel was clearly demonstrated by passing a brisk stream of laboratory air through the chemically quiescent reaction mixture, upon which polymerisation took place rapidly. A typical time–temperature curve for a reaction induced by laboratory air is given in Fig. 3.

Suspicion naturally fell on the moisture content of laboratory air as the activating agent for reaction, as it is well known that in some reactions Friedel–Crafts catalysts are active only in

the presence of water (see Hickinbottom, *Nature*, **1946**, **157**, 520; Heldman, *J. Amer. Chem. Soc.*, 1944, **66**, 1786; Leighton and Heldman, *ibid.*, **1943**, **65**, 2276; Heldman and Thurmond, *ibid.*, 1944, **66**, 427). That water is in fact the active agent was demonstrated by several experiments, the results of which are summarised in Table III. For instance, it was found that the passage of carefully dried oxygen, nitrogen, or atmospheric air through the reaction mixture does not induce reaction; on the other hand, moist air and moist nitrogen did act as promoters.

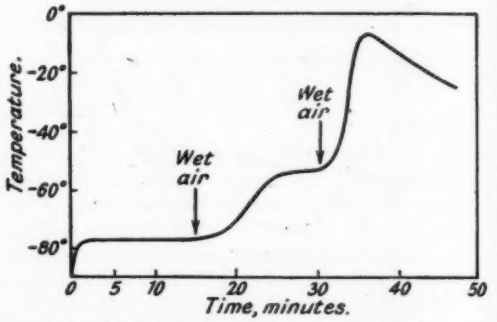
To be effective, laboratory air or moistened inert gases must be passed through for a certain time, at a sufficiently high rate. Positive effects were invariably found on passing atmospheric air for 1 minute at a rate of 3 l./min.: but the passage of the same quantity of air at the slower rate of 0·4 l./min. proved much less effective. An " effective " dose of laboratory air bubbled through at — 80° (passage for 1 min. at 2 l./min.) sometimes proved insufficient to drive the reaction to completion, but treatment with a second dose of air usually restarted the reaction and carried it to completion (see Fig. 4). It is noteworthy that the effect of the second dose was usually stronger than that of the first, probably owing to the higher temperature of the reaction mixture when the second dose was given.

FIG. 3.



Expt. 86. *Catalyst added at time* = 0. *At time* = 120 *mins.*, 3 *l. of laboratory air were blown through the chemically quiescent reaction mixture in* 1 *min.*

FIG. 4.



Expt. 81. *Catalyst added at time* = 0. *At time* = 15 *mins. and* 30 *mins.*, 4 *l. of laboratory air were passed through the reaction mixture in* 1 *min.*

The addition of small quantities of water in bulk form, as liquid, snow, or ice, to the reaction mixture did not initiate polymerisation. If the *iso*butene–hexane mixture at — 80° was treated with moist air before the addition of the catalyst, the subsequent addition of catalyst induced immediate reaction. This establishes a link with the preliminary experiments reported above.

Several experiments were carried out in an effort to find out whether or not polymerisation can be induced in the quiescent solutions by substances other than laboratory air or moistened inert gases. These experiments are quoted in Table III. As regards these substances the table shows that: (*a*) Hydrogen chloride is ineffective whether passed through the mixture at 1 atm. pressure, or at low partial pressures in admixture with dry nitrogen. (*b*) The results with carbon dioxide on the whole suggest that it is inactive, but are perhaps not quite conclusive. The slight positive effect obtained on one occasion was probably caused by incomplete removal of moisture from the gas. (*c*) The effect of ammonia is limited to combination with the catalyst: if the ammonia is added in small quantities only, subsequent addition of moist air allows reaction to proceed normally. Sulphur dioxide seems to behave in like manner. (*d*) Alcohol and ether, even when applied in small quantities, seem to prevent the initiation of polymerisation on the subsequent addition of moist air. They may be regarded as true poisons.

These results refer to reactions in which the starting temperatures were above — 90°. Experiments in which the catalyst was added to mixtures cooled to the lower range of temperature (— 90° to — 120°) gave inconclusive results. On the other hand, we have found that the quiescent state obtained on addition of catalyst to the mixture at — 60° is not disturbed by rapidly cooling this mixture down to — 120°, and that the passage of moist air then initiates polymerisation. In such cases we observed a considerable time lag (10—15 mins.) from the moment of passage of the moist air until the attainment of the maximum rate of reaction, so that the resulting time–temperature curves are markedly S-shaped (see Fig. 5). This shape is generally observable in the time–temperature curves for reactions initiated by moist air, but the

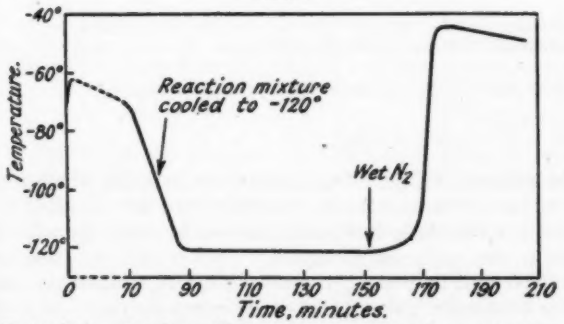
TABLE III.

Effect of substances added to the quiescent reaction mixture.

Substance (X) added.	Partial pressure of X (mm. Hg).	Rate of throughput (l./min.).	Time of throughput (mins.).	Observed effect.
O_2	760	4	1	Nil
N_2	760	4	1	Nil
Dry air	760	4	1	Nil
CO_2/N_2	10	3	1	Nil
	25	3	1	Nil
	500	3	1	Slight + ve
HCl	760	?	1	Nil
HCl/N_2	30	3	1	Nil
SO_2/N_2	15	3	1	Nil
NH_3	760	2	1	Temp. rise due to reaction with catalyst. No polymer
NH_3/N_2	40	2	1	Nil
$EtOH/N_2$	12	3	1	Poison
EtOH	0·1 c.c. (liquid)	—	—	Poison
Et_2O	0·25 c.c. (liquid)	—	—	Poison
H_2O	1 c.c. (liquid)	—	—	No effect
H_2O/N_2	17—20	2	1	+ ve
,, ...	4—5	4	1	+ ve
,, ...	17—20	0·6	1	No effect at −80°
,, ...	17—20	0·6	1	Slight + ve at −50°

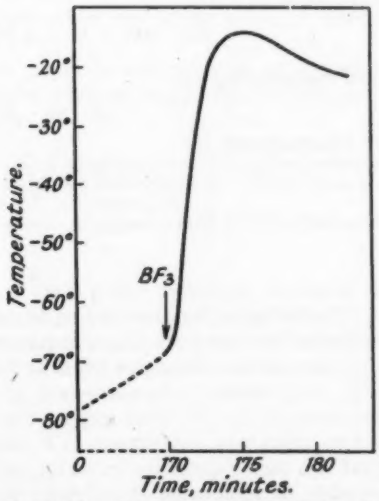
upward bend of the S is much sharper at higher starting temperatures, and there is no appreciable time lag before reaction sets in.

FIG. 5.



Expt. 104. *Catalyst added at time* = 0. *At time* = 70 *mins. air was admitted to the space between double walls of the reaction vessel. At time* = 88 *mins. the air space was re-evacuated. At time* = 150 *mins.* 3 *l. of nitrogen saturated with water vapour at room temperature were passed through the reaction mixture in* 1 *min.*

FIG. 6.



Expt. 88. *Catalyst added at time* = 0. *At time* = 170 *mins.* BF_3 *at atm. pressure was passed through the reaction mixture for* 1 *min.*

Discussion.—The discovery of the effect of moist air in the reactions catalysed by titanic chloride necessitates a re-evaluation of the earlier experimental results. The positive results obtained in our preliminary experiments were clearly due to the flow of air into the reaction vessel, and the lack of reproducibility was partly due to the fact that this inflow was uncontrolled. Similar remarks apply to Fairbrother and Seymour's experiments using titanic chloride. For the more powerful catalysts, such as boron trifluoride and aluminium bromide, definite evidence is yet lacking as to whether water is a necessary promoter of their catalytic activity. In the case of boron trifluoride we have indications that the critical water concentration is at any rate very much less than for titanic chloride. Davies (Thesis, Manchester, 1941) found that the careful exclusion of moisture from the boron trifluoride–*iso*butene system did not prevent rapid polymerisation; and we have observed that the addition of the trifluoride to a quiescent mixture

of *iso*butene and titanic chloride at — 80° brought about an immediate and rapid polymerisation (see Fig. 6). It may seem, on the other hand, plausible to generalise from the example of titanic chloride to all the weaker catalysts; but this point has not yet been investigated. In any case the gradation in the catalytic activity of different halides observed by Fairbrother and Seymour seems not to require alteration, for it is unlikely that there were marked differences in water accessibility in the course of the comparative experiments of these workers.

The action of water in the titanic chloride polymerisation is paradoxical, for water at temperatures of — 60° to — 80° can be present only in the solid phase, its solubility in hexane at such temperatures being only of the order of 10^{-10} g.-mol/l. Since the addition of liquid water to the reaction vessel, giving lumps of ice in the reaction mixture, was not able to start polymerisation, it seems essential that the water be present as an extremely fine dispersion, as might be expected to result from a rapid bubbling of moist air through a liquid at a very low temperature. The ineffectiveness of too slow a stream of moist air may be due to the fact that the slow through-put rate allows the moisture to condense in the delivery tube, so that it does not reach the reaction mixture, or at least not in the required state of fine dispersion. The active dispersion may be molecular, the water molecules being brought to react with titanic chloride at the liquid surface; or else a fine colloidal dispersion of ice may be formed.

We conclude that water, in some highly disperse state, can act as a chain starter in combination with titanic chloride for the polymerisation of *iso*butene. A possible mechanism of the reaction would then be:

$$\text{(i)}\quad TiCl_4 + H_2O \longrightarrow TiCl_4{\cdot}OH_2{}^*$$

$$\text{(ii)}\quad TiCl_4{\cdot}OH_2{}^* + M \longrightarrow \overset{+}{M}H + TiCl_4\bar{O}H$$
$$(M = \text{monomer} = CH_2{:}CMe_2.)$$

extending to

$$\text{(iii)}\quad \overset{+}{M}H + M \longrightarrow M_2\overset{+}{H} \qquad \text{(iv)}\quad M_2\overset{+}{H} + nM \longrightarrow M_{n+2}\overset{+}{H}$$
$$(M_n = \text{polymer.})$$

and terminating by

$$\text{(v)}\quad M_{n+2}\overset{+}{H} + TiCl_4\bar{O}H \longrightarrow M_{n+2} + TiCl_4{\cdot}OH_2$$

or alternatively by

$$\text{(vi)}\quad M_{n+2}\overset{+}{H} + TiCl_4\bar{O}H \longrightarrow M_{n+2}H{\cdot}OH + TiCl_4.$$

We may add to this scheme by including the possibility of chain transfer in the sense:

$$\text{(viii)}\quad M_n\overset{+}{H} + M \longrightarrow M_n + \overset{+}{M}H$$

The initiator is presumed to be the acid hydrate, $TiCl_4{\cdot}OH_2{}^*$, in which the asterisk is added to indicate that the initiating complex may be in an active state by carrying the heat liberated by (i). In the case of termination by (vi), and if we exclude the possibility of the chain transfer in (vii), each water molecule would give rise to one polymer molecule. This is still the case for termination by (v), if we impose the condition that only the activated $TiCl_4{\cdot}OH_2{}^*$ molecules can act as initiators. Although it is too early to discuss these possibilities much further, we note that the molar quantity of water added to initiate polymerisation was of the same order as the number of molecules of polymer formed, but it seems unlikely, in the circumstances of the experiments, that each water molecule introduced could enter into reaction. Moreover, the observation that the addition of an "effective" dose of moist air sometimes resulted in an incomplete reaction (see Fig. 4) certainly suggests that a molecule of water cannot continue to produce new chain centres indefinitely. Possibly the water is removed and rendered inactive by precipitation of the $TiCl_4{\cdot}OH_2$ molecules from solution or by their decomposition to give $TiOCl_2$.

The efficiency of titanic chloride as catalyst in *initiating* the polymerisation is clearly dependent upon the acid strength of the $TiCl_4{\cdot}OH_2$ complex. If a scheme of the type outlined for titanic chloride is applicable to the polymerisation of *iso*butene by Friedel–Crafts catalysts in general, it seems likely that the activity of these catalysts will be directly proportional to the acid strengths of their hydrates. Reliable measurements by independent methods of the acid strengths of the various catalysts in the Friedel–Crafts group are not yet available, although we understand from Dr. Fairbrother (who is at present engaged upon this problem) that without question the acid strengths of the strong catalysts such as BF_3 and $AlBr_3$ are markedly greater than those of the weaker catalysts such as $SnCl_4$. The same point is made by Martin (*Chem.*

Reviews, 1944, **34**, 461) in respect of the relative acid strengths of BF_3 and BCl_3 in a review of the power of these two compounds to form complexes.

Similarly the efficiency of titanic chloride as *terminator* should be related to the base strength of the complex anion $TiCl_4\bar{O}H$, and in the general case of Friedel–Crafts catalysts, the terminator efficiency should be related to the base strength of the anions $MX_n\bar{O}H$. This quantity is *inversely* proportional to the acid strength of the complex $MX_n{\cdot}OH_2$, so that the more active the catalyst as initiator, the less active will it be as terminator. It follows immediately from this that the polymer molecular weight should be greater the more effective, *i.e.*, the stronger, the catalyst. We have previously drawn attention to the experimental evidence confirming this point, given in Table I.

The suggested mechanism of polymerisation would be liable to inhibition by bases, but in view of the strong acid properties of the catalyst, it might be expected that the addition of a base would merely neutralise the catalyst, and reduce to that extent its effective concentration. This seems to be the case for ammonia and sulphur dioxide.

It is curious that alcohol and ether cannot replace water in starting polymerisation, and still more remarkable that, when added in small quantities, they prevent the normal action of water. A similar poisoning effect was found by Miss Mandel (Thesis, Manchester, 1943) in the *iso*butene polymerisation with aluminium bromide, which is inhibited by the addition of acetone, and by the complex $2AlBr_3{,}COMe_2$. We postpone discussion of these points until more evidence is available.

The S-shaped time–temperature curves also present a difficulty to the proposed mechanism. They may signify the presence of a poison which is removed during the preliminary stage of the reaction. Or alternatively, they may be explained by postulating a " chain-branching " phenomenon, similar to that suggested by Semenov in respect of explosive gas reactions: in this case the carbonium-ion mechanism would require amplification by some kind of energy chain.

The experimental work described in this paper is still in progress, and we hope to be able to elaborate the theory and clarify some of its obscure points later when we have more experimental data.

The authors are indebted to the Research Laboratories of I.C.I., Billingham, for the original stimulus to this investigation and for supplying them with *iso*butene of the requisite quality. They were also assisted by grants from the D.S.I.R. and from the Anglo-Iranian Oil Company Ltd.

Discussion.

PROF. M. G. EVANS: (1) Professor Polanyi reports a very great difference between the catalytic effect of water and that of hydrogen chloride in the presence of metal halides of the type $AlCl_3$. If the proton is the catalytic agent in the polymerization of *iso*butene, the difference in the action of water and hydrogen chloride should be revealed in the energetics of the reactions:

$$MCl_3 + ClH \longrightarrow MCl_4^- + H^+$$
$$MCl_3 + HOH \longrightarrow MCl_3OH^- + H^+$$

The energy changes involved in these reactions are respectively

$$-D_{HCl} - I_H + E_{Cl} + S_{Cl^-}$$
$$-D_{HOH} - I_H + E_{OH} + S_{OH^-}$$

in which D is the bond strength of the molecules, I_H the ionization potential of the hydrogen atom, E the electron affinity of the chlorine atom or the OH radical, and S the solvation energy of the Cl^- or OH^- ion by the metal halide MCl_3.

The ratio of the dissociation constants K_1 and K_2 will be given by $\ln K_1/K_2 = (Q_1 - Q_2)/RT$, and at the temperature of these experiments, *viz.*, 100° K., a value of $(Q_1 - Q_2) = -4{\cdot}6$ kg.-cals. will lead to a value of $K_1/K_2 = 10^{-10}$. Using the following values: $D_{HCl} = 4{\cdot}45$, $D_{HOH} = 4{\cdot}77$, $E_{Cl} = 3{\cdot}78$, $E_{OH} = 2{\cdot}04$ electron volts, the value of $(Q_1 - Q_2) = -4{\cdot}6$ kg.-cals. would necessitate a value of $(S_{OH^-} - S_{Cl^-}) = 1{\cdot}62$ e.v. This is not an unreasonable value; the difference in the heats of solvation of Cl^- and OH^- in water is 1·87 e.v.

The catalytic action of both water and hydrogen chloride with aluminium chloride in the isomerization reactions of hydrocarbons seems now to be well established. These reactions which are attributed to a proton attack occur, however, at relatively elevated temperatures

where the value of $(Q_1 - Q_2)$ will not be so important in differentiating between the action of water and of hydrochloric acid.

(2) The influence of the stability of the active ending of a growing polymer chain upon the structure of the polymer chain is not peculiar to an ionic active ending. Thus in a radical-polymerization reaction the energy change E of a polymerization step will depend upon the resonance energies R_a and R_f of the attacking radical and the radical formed :

$$E = - D_{C=C} + D_{C-C} - R_a + R_f$$

For " head-to-tail " polymerization, when the attacking radical is identical with that formed as a result of the chain-propagation step, $R_a = R_f$ and $Q = - D_{C=C} + D_{C-C}$.

For " head-to-head " reaction followed by a " tail-to-tail " step the energy changes of the successive reactions will be

$$E_1 = - D_{C=C} + D_{C-C} - R_a + R_f$$
$$E_2 = - D_{C=C} + D_{C-C} + R_a - R_f$$

and hence the heat of reaction will alternate from step to step by an amount $2R_a - 2R_f$ and will influence in a similar way the activation energy of reaction.

FIG. 1.

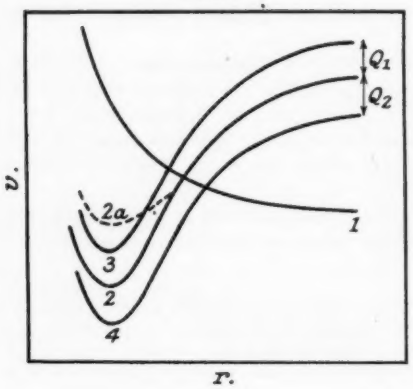
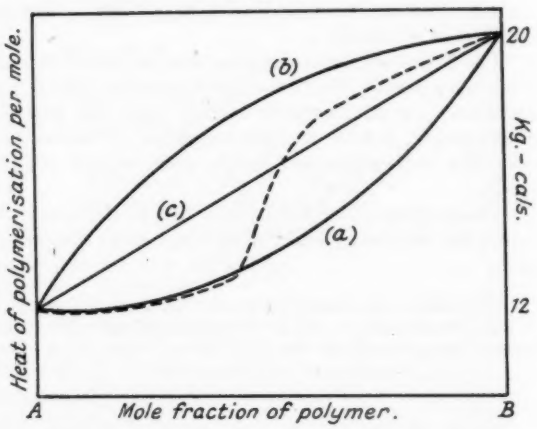


FIG. 2.



That difference in the resonance energy of radicals is sufficient to give rise to selectivity in the opening of a double bond is seen in the " Karasch effect ". In this case the increased stability of $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C\!-\!CH_2X$ as compared with $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!\overset{X}{C}\!-\!CH_2-$ gives rise to the reversal of the " Markownikov rule ".

It is surprising that *iso*butene can be polymerized by an ionic initiator and not by a free radical. Fig. 1 shows diagramatically the change in potential energy involved in a chain-propagation step.

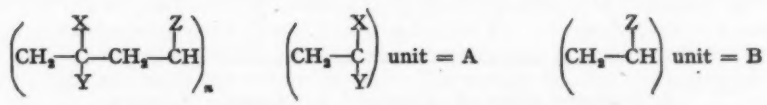
Curve 1 represents the change in potential energy with r for the bond assignment $\sim\sim\sim CH_2-CH_2\overset{r}{\cdots}CH_2=CH_2$, and Curve 2 that of $\sim\sim\sim CH_2-CH_2\overset{r}{-}CH_2-CH_2$.

Curve 2a is the corresponding curve to 2 when " steric energy " effects are present, and Curves 3 and 4 correspond to the two cases in which $R_a \neq R_f$, $Q_1 = Q_2 = (R_a - R_f)$.

The potential-energy diagram for an ionic reaction will in the main differ from the above in the magnitude of Q_1 and Q_2; $Q_1 = Q_2 = (I_a - I_f)$ (in which I refers to the ionization potentials). We would conclude, therefore, that in an ionic polymerization reaction the larger value of $(I_a - I_f)$ compared with $(R_a - R_f)$ for radical reaction would lead to greater *differences between the activation energies* of head-to-head, tail-to-tail, and head-to-tail polymerization steps.

(3) *Heats of polymerization.* Professor Polanyi and his co-workers have shown that the repulsion energy between the side groups in a polymer chain of the type $\left(-CH_2-\overset{X}{\underset{Y}{C}}-\right)_n$ leads

to a reduction in the heat of polymerization. In Leeds we have studied the influence of such side groups as X = Y = Cl; X = CH_3, Y = CO_2R (in which R is CH_3,C_6H_{13},$C_{10}H_{23}$) on the heat of polymerization and found results similar to those of Polanyi. An interesting extension of this is to be found in the heat of copolymerization of a di- and a mono-substituted monomer :



There are three extreme possibilities : (*a*) that the polymer is a random distribution of A's and B's and the heat of an A–B link is equal to that of A–A; (*b*) that the heat of an A–B link is equal to that of B–B; and (*c*) that the co-polymer is built up of large units of A polymer and B polymer, thus $-[A-A]_n-A-B-[B-B]_m$.

Fig. 2 shows the heat of polymerization per mole as a function of the composition of the polymer for these three cases. Preliminary results obtained for the co-polymer of methyl methacrylate and acrylonitrile lie approximately on the dotted line of Fig. 2.

From these results it would appear that a CH_2—$\underset{\displaystyle Y}{\overset{\displaystyle X}{C}}$ unit flanked by CH_2—$\overset{\displaystyle Z}{CH}$ units is under less constraint than when flanked by CH_2—$\underset{\displaystyle Y}{\overset{\displaystyle X}{C}}$, and hence the heat of the A–B link approaches that of B–B, whereas a CH_2—$\overset{\displaystyle Z}{CH}$ unit when flanked by CH_2—$\underset{\displaystyle Y}{\overset{\displaystyle X}{C}}$ units is under constraint from the neighbouring side groups and hence the heat of A–B approaches that of the A–A.

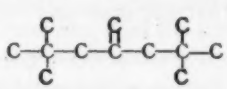
T. A. Kletz and W. C. Price : *The infra-red spectra of butene trimer and tetramer.* We have had the opportunity of examining the infra-red spectra of the butene trimer and tetramer referred to by Professor Polanyi in his opening paper. This provides an interesting application of the principles discussed by Dr. H. W. Thompson in his paper on the infra-red spectra of macromolecules.

The original materials were believed to be mono-olefins. After their infra-red spectra had been recorded, they were hydrogenated and the spectra of the hydrogenated material also obtained. The spectra of the unsaturated trimer and tetramer in the region 5—15 μ show the following points of interest. First, the spectra of both trimer and tetramer are rather similar, indicating that the basic sub-groupings in both molecules are the same. Both trimer and tetramer have strong bands in the neighbourhood of 1200 and 1237 wave-numbers which indicate the presence of terminal *tert.*-butyl groups. The intensity of these bands compared with the corresponding bands in the spectrum of 2 : 2 : 4-trimethylpentane suggests at least two *tert.*-butyl groups per molecule. The absence of bands in the region 1163—1176 wave-numbers shows that there is no terminal *iso*propyl group, while the absence of a band at 1136 wave-numbers shows there are no adjacent tertiary carbon atoms. The presence of non-adjacent internal tertiary carbon atoms is not excluded.

Both samples show the frequency of the C=C bond at 1650 wave-numbers. The trimer has a well-defined band at 893 and the tetramer at 897 wave-numbers, indicating that the double bond is of the type $CR_1R_2{:}CH_2$. The tetramer has an additional strong band at 859 wave-numbers, but it has not yet been possible to correlate this with any special structural feature.

The infra-red spectra of the hydrogenated trimer was found to be identical with that of a sample isolated from the high-boiling residue from an *iso*octane plant. This specimen had been identified by its physical data (b. p. 178·3, $n_D^{20°} = 1{\cdot}4200$) with 2 : 2 : 4 : 6 : 6-pentamethylheptane (b. p. 174—175°, $n_D^{20°} = 1{\cdot}4199$) and its infra-red spectrum—first obtained by Sutherland and Willis—strongly supports this identification.

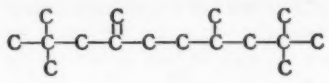
This information, taken together with that on the unsaturated compound, points to the structure :



for the trimer. This formula is consistent with the inability of the molecule to polymerise further, as the *tert.*-butyl groups protect the double bond.

The spectrum of the saturated tetramer is almost identical with that of the saturated trimer, showing that it must contain very similar groupings.

A formula for the unsaturated tetramer which is consistent with all the evidence is :



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3. *Polymerisation of Monomers in Aqueous Solution.*

By M. G. Evans.

It has now been well established that free radicals or reactions yielding free radicals are able to initiate the polymerisation of unsaturated monomers both in the gas phase and in the liquid monomer phase; such initiating reactions can be written :

$$R + CH_2{=}\underset{X}{CH} \longrightarrow R{-}CH_2{-}\underset{X}{CH}-$$

and the free radical thus formed can undergo a similar reaction with another monomer molecule :

$$R{-}CH_2{-}\underset{X}{CH}- + CH_2{=}\underset{X}{CH} \longrightarrow R{-}CH_2{-}\underset{X}{CH}{-}CH_2{-}\underset{X}{CH}-$$

There are a number of reactions in aqueous solution in which free radicals or free radical ions are probably produced as intermediates in a reaction sequence. These reactions are usually electron-transfer reactions; *e.g.*,

(1) $Fe^{++} + H_2O_2 \longrightarrow Fe^{+++} + HO^- + OH$; $Fe^{++} + OH \longrightarrow Fe^{+++} + OH^-$

(2) Quinone $+ e \longrightarrow$ Semiquinone; Semiquinone $+ e \longrightarrow$ Quinone ion

The free radicals or radical ions are formed in the above cases because electron-transfer reactions, involving a change of two or more electrons, occur as a sequence of one-electron transfer steps. A preliminary investigation showed that such reactions were very effective in initiating polymerisation reactions with monomers such as methyl methacrylate, methacrylic acid, methyl acrylate, acrylonitrile, styrene, vinylidine chloride, etc., in aqueous solution. The system ferrous ions–hydrogen peroxide was much more effective, *i.e.*, it led to a much more rapid formation of polymer, than was hydrogen peroxide alone.

In the absence of a polymerisable monomer, ferrous ions in excess of hydrogen peroxide catalyse the decomposition of hydrogen peroxide leading to the evolution of oxygen. Haber and Weiss (*Proc. Roy. Soc.*, **1939**, *A*, **147**, 332) put forward the following reaction sequence to account for this overall reaction :

$$H_2O_2 + Fe^{++} \longrightarrow HO^- + OH + Fe^{+++}$$
$$HO + Fe^{++} \longrightarrow HO^- + Fe^{+++}$$
$$HO + H_2O_2 \longrightarrow H_2O + HO_2$$
$$HO_2 + H_2O_2 \longrightarrow HO + H_2O + O_2$$

In the presence of a polymerisable monomer we found that the evolution of oxygen could be very considerably reduced or even stopped.

This observation means that the monomer molecules are reacting with the chain carriers and that this reaction leads, not only to a breaking of the chain of events leading to oxygen evolution, but also to the polymerisation of the monomer.

The Stoicheiometry of the Reaction between Ferrous Ions and Hydrogen Peroxide in the Absence and in the Presence of Monomers.—The preliminary observations referred to above can be explained on the basis of the Haber–Weiss mechanism for the reaction between ferrous ions and hydrogen peroxide, if we postulate that the hydroxyl radical attacks the double bond of the monomer thus :

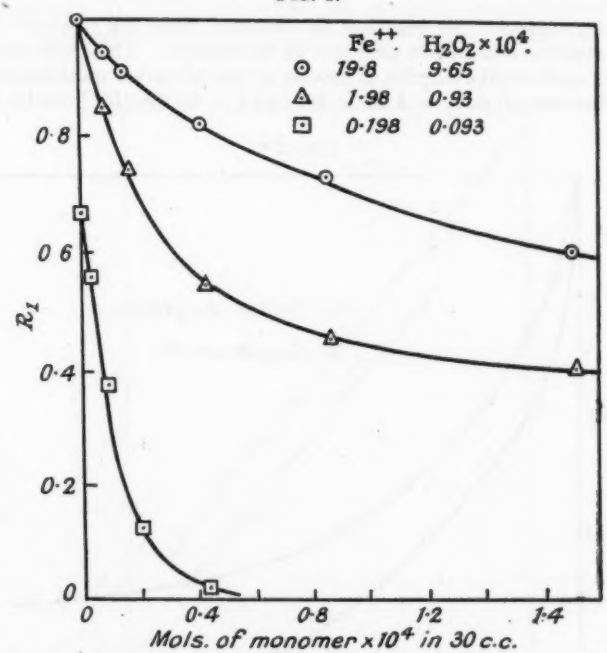
(I) $H_2O_2 + Fe^{++} \longrightarrow HO + OH^- + Fe^{+++}$

(II) $HO + Fe^{++} \longrightarrow HO^- + Fe^{+++}$

(III) $HO + CH_2{=}\underset{X}{CH} \longrightarrow HO{-}CH_2{-}\underset{X}{CH}-$

This idea has been tested by a study of the stoicheiometry of the reaction in the absence and in the presence of monomers. When the molality of ferrrous ions is equal to or in excess of that of the hydrogen peroxide, the reaction in the absence of monomer is limited to reactions (I) and (II) and the stoicheiometry of the reaction corresponds to 1 mole of H_2O_2 = 2 moles of ferrous ions. If, however, reaction (III) occurs, then since reactions (II) and (III) are in competition for the OH radicals produced in step (I), the presence of monomer should lead to a deviation in stoicheiometry from 1 mole H_2O_2 = 2 mole Fe^{++} towards that of 1 mole H_2O_2 = 1 mole Fe^{++}. Fig. 1 shows the effect of monomer concentrations on the stoicheiometry, and the changes are consistent with the above scheme. Increasing the concentration of ferrous ions

FIG. 1.



Effect of initial Fe^{++} *concentration on the value of* R_1 *in the presence of methyl acrylate, where* $R_1 = \frac{[Fe^{+++}]_t - [H_2O_2]}{[H_2O_2]_0}$.

necessitates a higher concentration of monomer to bring about a given change. Fig. 2 shows that different monomers react with OH radicals at different rates and hence compete to different extents with reaction (II). All the reactions so far reported in this section were carried out in an atmosphere of nitrogen. It was found that the presence of oxygen gave rise to long induction periods in the polymerisation, and with sufficiently low concentrations of reactants suppressed it altogether; further, that in a system in which reactions (I), (II), and (III) were taking place oxygen was absorbed and the amount absorbed was measured.

Wieland and Franke (*Annalen*, 1927, **457**, 1; 1929, **459**, 1; see also Fenton *et al.*, *J.*, 1894, **65**, 899; 1900, **77**, 69) showed that hydrogen peroxide, together with catalytic amounts of ferrous ions, forms an effective oxidising system for organic substrates such as lactic and glycollic acids, alcohols, etc. Systems were therefore studied in which both a polymerisable monomer and an oxidisable substrate were present, and the results showed that polymerisation and oxidation were competing reactions and that the presence of a large amount of monomer reduced very considerably the oxidation of the glycollic or lactic acid by the hydrogen peroxide–ferrous ion system. It would appear probable, therefore, that the same entity is responsible for the opening of the double bond of the monomer and for initiating the oxidation chain of the glycollic acid:

$$HO + CH_2{=}\underset{\displaystyle X}{CH} \longrightarrow HO{-}CH_2{-}\underset{\displaystyle X}{CH}{-} \longrightarrow \text{polymerization}$$

$$HO + HR \longrightarrow HO_2 + R \longrightarrow \text{oxidation}$$

The Kinetics of the Hydrogen Peroxide–Ferrous Ion Reaction.—The rates of formation of ferric ions in the absence and in the presence of monomers have been measured, colorimetric methods being used for determining the concentration of ferrous and ferric ions. The kinetics in the absence of monomers arise from reaction (I) and (II), whereas in the presence of a large excess of monomer reaction (II) is suppressed completely. Table I gives a comparison of the

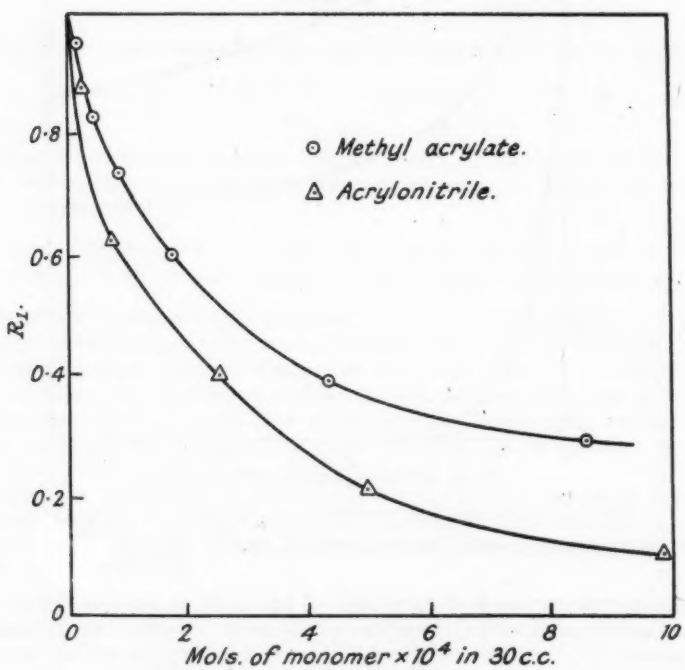
TABLE I.

Absence of monomer (k_1 25°)	61	59	59	67	67	56
Presence of monomer (k_1 25°)	58	55	49	72		
Concn. of monomer, moles/l.	0·070	0·070	0·065	0·25		

values of the velocity constant for reaction (I) obtained from the different kinetic expressions which arise in the absence and in the presence of monomers. The close correspondence of the two sets of results is additional evidence in favour of the proposed mechanism.

The value of k_1 for step (I) is $k_1 = 1{\cdot}78 \times 10^9 \exp.\{-10{,}000/\boldsymbol{R}T\}$ (moles/l.)$^{-1}$ sec.$^{-1}$.

FIG. 2.*



* For definition of R_1, see Fig. 1.

The Kinetics of Polymerisation.—The whole reaction scheme proposed for the polymerisation of aqueous solutions of monomers is:

$$Fe^{++} + H_2O_2 \longrightarrow Fe^{+++} + HO^- + OH \quad . \quad . \quad . \quad k_1$$

$$HO + M \longrightarrow HO{-}M{-} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_i$$

$$\left.\begin{array}{l} HOM{-} + M \longrightarrow HO{-}M{-}M{-} \\ \cdot\ \cdot\ \cdot \qquad \cdot\ \cdot\ \cdot \\ HO(M)_n{-} + M \longrightarrow HO(M)_{n+1} \\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot \qquad \cdot\ \cdot\ \cdot \end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad k_p$$

$$HO(M)_n{-} + {-}(M)_mOH \longrightarrow HO(M)_{n+m}OH \quad . \quad . \quad . \quad . \quad . \quad k_t$$

$$HO(M)_n + OH \longrightarrow HO(M)_nOH \quad . \quad . \quad . \quad . \quad . \quad . \quad k'_t$$

Two possible chain-termination steps are given, one resulting from the mutual interaction of growing polymer chains, and the other from the reaction between a growing polymer chain and an hydroxyl radical.

Assuming that k_p and k_t are independent of chain length and employing stationary-state conditions, we have the relation between monomer concentrations and time t:

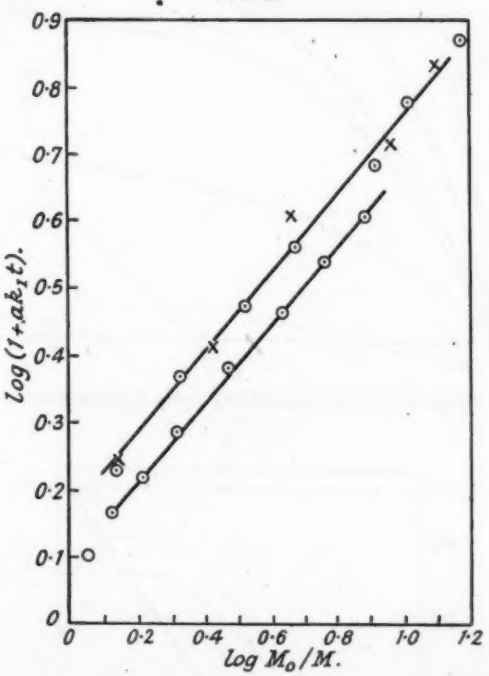
$$\log \frac{M}{M_0} = \frac{k_p}{\sqrt{k_1 k_t}} \log (1 + ak_1 t) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

for mutual termination, in which a is the molality of both ferrous ions and hydrogen peroxide and M_0 is the initial concentration of monomer. For hydroxyl-radical termination the expression is

$$\frac{1}{M} - \frac{1}{M_0} = \frac{k_1 k_p}{k_t} \cdot t$$

Fig. 3 shows that equation (1) fits the experimental results for methyl methacrylate, and that the slope $k_p/\sqrt{k_1 k_t}$ is independent of both M_0 and initiator concentration a.

FIG. 3.



Although the monomers are in aqueous solution, the polymer produced is insoluble, so it was not surprising to find that added emulsifying agents had a profound effect upon the rate of polymerisation. Fig. 4 shows the effect of trimethylcetylammonium bromide on the rate of polymerisation. The emulsifying agent does not change the mechanism of reaction; at all concentrations of emulsifying agent the kinetics obey equation (1), but the value of $k_p/\sqrt{k_1 k_t}$ increases with increasing concentration of emulsifying agent.

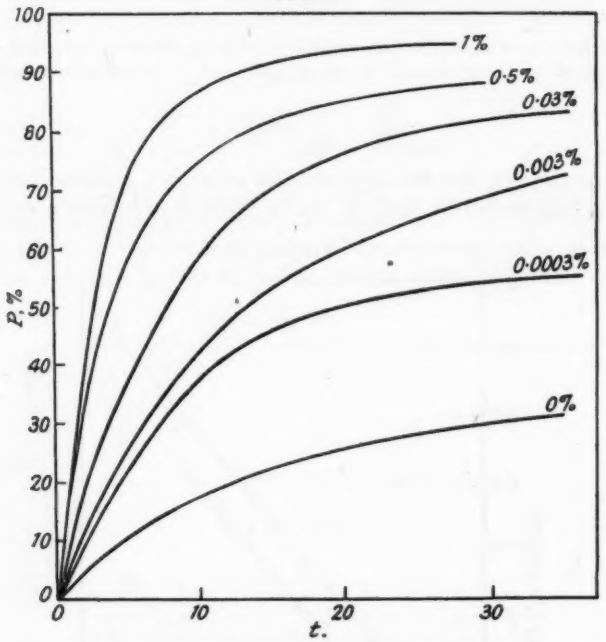
This is not an effect upon k_1 which is found to be independent of emulsifying agent concentration. Measurements at different temperatures lead to a value of $(E_p - \frac{1}{2}E_t)$, in which E_p is the activation energy of the propagation step and E_t that for the mutual termination reaction: $E_p - \frac{1}{2}E_t = 5000$ cals./mole, and this value is practically independent of emulsifying agent concentration.

Molecular Weights and their Distribution.—The reaction scheme outlined above leads to a very simple connection between the reaction conditions and the mean number molecular weight. The number of moles of polymer formed in a reaction is equal to one-half the number of moles of hydrogen peroxide used, since each polymer molecule contains two OH groups each of which originated from one hydrogen peroxide molecule. Thus if a is the amount of hydrogen peroxide used in the reaction and ΔM is the amount of monomer polymerised

$$\bar{N} = 2\Delta M/a$$

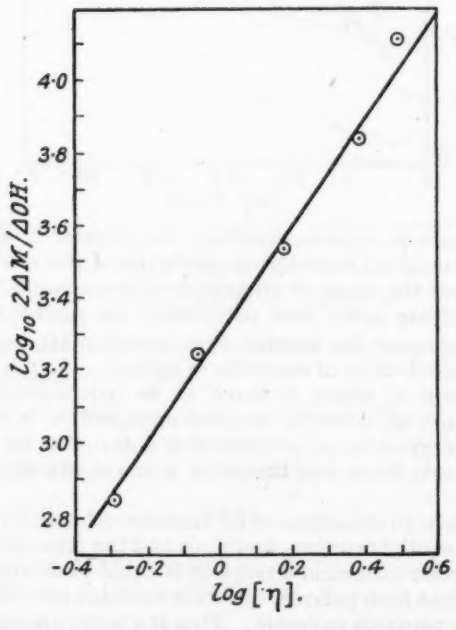
In Fig. 5 the value of log $(2\Delta M/a)$ is plotted against log $[\eta]$ (where $[\eta]$ is the intrinsic viscosity of the polymer) for a series of different reaction conditions, methyl methacrylate being used

FIG. 4.



Effect of varying emulsifying agent concentration.

FIG. 5.



as the monomer, and it is seen that the mean number molecular weight and the intrinsic viscosity are related by

$$\log (2\Delta M/a) = \log K + a \log [\eta]$$

In order to obtain a much better test of the above reaction scheme, the distribution of molecular weights has been calculated on the basis of the kinetics, and the results compared with those obtained by fractionation and osmotic measurements.

Using the methods outlined by Gee and Melville (*Trans. Faraday Soc.*, 1935, **32**, 54) and by Herrington and Robertson (*ibid.*, 1942, **38**, 490; Herrington, *ibid.*, 1944, **40**, 236), one can calculate the distribution of molecular weights from the kinetics. This is possible because the kinetics of the reactions leading to initiation of polymerisation are known. This leads to an expression

$$\frac{dP_N}{dM} = \tfrac{1}{2}\frac{a^2\beta^2}{M^3}\left(\frac{M_0}{M}\right)^{-3\beta}(N-2)\left\{1+\frac{a\beta}{M}\left(\frac{M_0}{M}\right)^{-\beta}\right\}^N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

in which P_N is the amount of polymer of chain length N, $\beta = \sqrt{k_1 k_t}/k_p$, M_0 the initial monomer concentration, and a the initiator concentration. Figs. 6 and 7 show the integrated form of

FIG. 6.

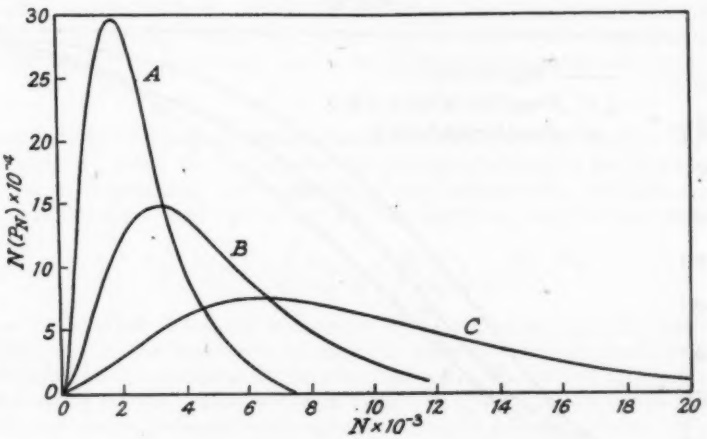
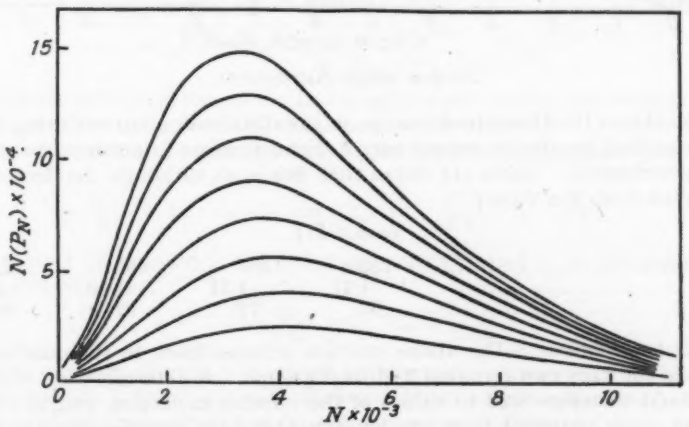


FIG. 7.



equation (3) for different values of a and at different stages in the reaction. Fig. 8 shows a comparison of the theoretical distribution curve with the experimental curves obtained by a single and a double fractionation. The molecular weights were determined from osmotic pressures. The agreement is good when one takes into consideration the difficulties of fractionation and molecular-weight determination.

A more striking comparison is afforded by the theoretical and experimental values of the viscosity chain length. This property is related to the distribution curve by

$$\bar{N}_v = \left[\frac{\Sigma w_i N_i^{1/a}}{\Sigma w}\right]^a$$

in which α is the exponent in relation between number molecular weight and intrinsic viscosity of sharp fractions, N_i the chain length, and w_i the weight of the ith species can be obtained from the theoretical distribution curve.

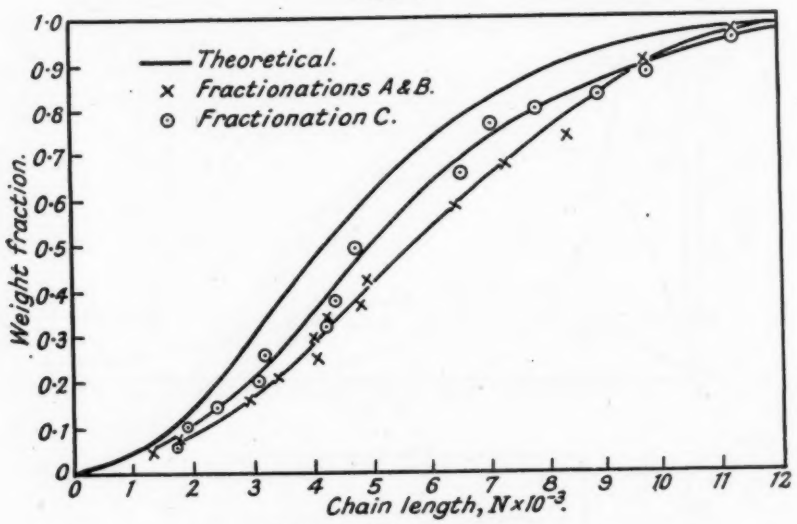
Table II compares the theoretical values of the viscosity average molecular weight with those determined experimentally for methyl methacrylate polymer samples produced under

TABLE II.

Concn. of initiator, moles/l.	2×10^{-4}	1×10^{-4}	$0{\cdot}5 \times 10^{-5}$
Viscosity mol. wt. Calc.	24,300	45,400	91,400
Viscosity mol. wt. Found	23,200	48,500	92,900

different conditions. Not only do the values change with initiator concentration in the way which one would expect, but the actual values compare very well with the theoretical values.

FIG. 8.



Integral weight distributions.

Fig. 7, which shows the theoretical change in the distribution curve during the course of a reaction, indicates that we should expect only a slight decrease in mean molecular weight with percentage polymerisation. Table III shows that this is so, although the decrease is less than would be predicted from the theory.

TABLE III.

Time, secs.	235	360	600	782
$[\eta]$	1·51	1·51	1·50	1·50
P, %	62	72	82	90

End-group Determinations.—The above reaction scheme leads to the conclusion that each polymer molecule contains two terminal hydroxyl groups. A determination of these groups in the polymer should therefore lead to values of the number molecular weight which should be comparable with those obtained from the kinetics and from osmotic-pressure measurements. The method we have used for the determination of hydroxyl groups is similar to that used by Bolland (*I.R.I. Trans.*, 1941, **16**, 267), based on the reaction between methylmagnesium chloride and a hydroxy-compound. We are very conscious of the fact that incomplete drying of these polymer samples formed in aqueous systems would completely vitiate the results, and extreme care has therefore been taken. The following are put forward only as preliminary results.

The polymer used for this comparison was polystyrene, and the results of end-group determination are compared with the value of the molecular weight M for unfractionated samples and with the molecular weight from osmotic-pressure measurements for fractionated

samples. The results (Table IV) show a fair agreement between the values of molecular weight obtained by the two methods.

TABLE IV.

M by end-group method.	*M*.	Method.	*M* by end-group method.	*M*.	Method.	*M* by end-group method.	*M*.	Method.
33,600	34,200	$2M/a$	86,300	97,000	Osmotic pressure	71,600	80,600	Osmotic pressure
40,600	34,200	$2M/a$	88,700	97,000		72,800	80,600	

The Values of k_p *and* k_t *and their Dependence upon Chain Lengths.*—In the kinetic treatment above it has been assumed that k_p and k_t are both independent of chain length, and the agreement between theory and experiment suggests that this is a valid assumption. Melville and Burnett (*Nature*, 1945, **156**, 661) have recently reported that in the case of bulk polymerisation of vinyl acetate both k_p and k_t are independent of chain length.

The transition states of both chain-propagation and chain-termination reactions are associated states, and it has been shown that for such cases the entropy change accompanying the formation of the transition state can be set equal to that of the formation of a final state of the same configuration. An investigation of the entropy changes of such reactions as

$$P_x + M \longrightarrow P_{x+1} \qquad P_{x_1} + P_{x_2} \longrightarrow P_{x_1+x_2}$$

will, therefore, help in understanding the temperature-independent factors of propagation and termination reactions, since we can equate the entropy changes of the above reactions to the entropy changes accompanying the formation of the corresponding transition states.

Many expressions have been developed for the partition functions of long-chain molecules in solution; *e.g.*,

$$F = f_0^{n_0} f_1^{N} \frac{1}{\sigma N} \frac{(n_0 + N)!}{n_0! \prod n_x!} \left(\frac{\gamma}{n_0 + N}\right)^{\Sigma(x-1)n_x}$$

in which n_0 is the number of solvent molecules, $N = \Sigma x n_x$ where n_x is the number of molecules of chain length x, σ is the symmetry number of units of solute molecules, f_0 and f_1 are the partition functions for the motions of solvent and solute molecules, and γ is the co-ordination number of the space lattice. This equation makes no distinction between the behaviour of a free monomer unit and a monomer unit incorporated in a polymer chain. If we consider that the monomer unit in a free state will be able to rotate and oscillate more freely than a unit in a polymer chain, then the equation must be modified to

$$F = f_0^{n_0} f_m^{N - \Sigma' x n_x} f_p^{\Sigma' x n_x} \frac{1}{\sigma N} \frac{(n_0 + N)!}{n_0! \prod n_x!} \left(\frac{\gamma}{n_0 + N}\right)^{\Sigma(x-1)n_x}$$

in which f_m is the partition function of the free monomer unit and f_p that of monomer units in the polymer chains, and the summation Σ' is taken over all values of x except $x = 1$. From this expression the standard entropy changes accompanying chain propagation and termination are respectively

$$\frac{\Delta S^\circ_p}{RT} = 1 - \log \gamma - \log f_m/f_p \quad \text{and} \quad \frac{\Delta S^\circ_t}{RT} = 1 - \log \gamma$$

when concentrations of monomers and polymers are expressed as moles per total number of moles of monomer units, *i.e.*,

$$C_x = \frac{n_x}{\Sigma x n_x} \quad \text{and} \quad C_m = \frac{n_m}{\Sigma x n_x}$$

Identifying these entropy changes with those between the corresponding initial and transition states, we see that both k_p and k_t are independent of chain length. Moreover, the temperature-independent factors for propagation and termination are related by

$$A_p/A_t = f_p/f_m$$

The value of $A_p/A_t = 10^{-3}$ found by Melville is understandable on the model that the monomer units in the liquid phase are free to rotate whereas in the polymer chain their motion is greatly restricted to a libration or vibration.

These ideas developed here are not, however, applicable to reactions in which the polymer chains are insoluble in the reaction medium, which is the case in polymerisation of aqueous solutions of monomers. Under such conditions, when the heat of solution of the polymer chains is a large negative quantity, the polymer chains will behave like lyophobic colloids. Termination

of polymerisation will occur by the coagulation of the active polymer chain with other active chains, and hence equations for the kinetics of colloidal coagulation might be applicable.

The velocity constant for coagulation of spheres of radii r_1 and r_2 is

$$k = \frac{8RT}{3000\eta}\left\{\frac{2 + r_1/r_2 + r_2/r_1}{4}\right\} \text{ (moles/l.)}^{-1} \text{ secs.}^{-1}$$

and if the polymer chains of length x are coiled up into spheres then in terms of chain length

$$k_t = \frac{8RT}{3000\eta}\left\{\frac{2 + (x_1/x_2)^{\frac{1}{3}} + (x_2/x_1)^{\frac{1}{3}}}{4}\right\} \text{ (moles/l.)}^{-1} \text{ secs.}^{-1}$$

The velocity constant is therefore only very slightly dependent upon chain length, being independent of chain length when $x_1 = x_2$, and is only increased by 4% when $x_1 = 10x_2$. It would appear justifiable therefore to consider k_t virtually independent of chain length.

The effect of added emulsifying agent upon the value of $\frac{k_p}{\sqrt{k_1 k_t}}$ can now be understood as an effect upon the coagulation constant k_t. An emulsifying agent such as trimethylcetylammonium bromide will be adsorbed on the polymer colloidal particle, setting up a Helmholtz double layer which will stabilise the colloidal system.

The work reported in this survey was carried out in collaboration with Mr. J. H. Baxendale, Mr. G. S. Park, Mr. J. H. Kilham, and Mr. S. Bywater.

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4. *Polymerisation of Vinyl Compounds in the Gas and in the Liquid Phase.*

By H. W. Melville.

This section of the discussion is confined to a review of the present position regarding the mechanism of polymerisation of ethylene derivatives in the liquid and in the gas phase at temperatures from 0° to 200°. A great deal of pioneering work has now established the following general points. The reactions are all of the chain type, though the possibility of non-chain processes is not excluded. The growth reaction always involves a bimolecular interaction of some kind of polymer molecule which is specially reactive, for example, a free radical, and a monomer. The size to which the polymer molecule grows is determined by the relative probabilities of the growth reaction and another reaction which removes the activity of the polymer. Kinetic analysis along conventional lines has indicated so far only two types of collision whereby the activity is destroyed. The first, and by far the most common, involves the participation of two active polymer molecules, a reaction which is readily explicable if the activity is a free valency. The second is apparently a special type of collision with the monomer but of a different nature from that occurring during propagation. This is a comparatively rare type of process and so far has only been observed in the gas-phase polymerisation of acetylene and of butadiene, the chain lengths in both reactions being comparatively small. A third type of growth-stopping process has been suggested, namely, the spontaneous loss of activity by the active polymer. No experimental evidence has yet appeared which supports such a mechanism. The only case where something of the kind occurs is in the photopolymerisation of vinyl acetate vapour. In this reaction the photo-excited monomer can, in fact, lose its energy spontaneously before the molecules of monomer add on. The loss of activity does not occur once the chain has started growing (Tuckett and Melville, unpublished). The activity can also be removed by intentionally added inhibitors. Occasionally it is difficult to remove very small traces of inhibitors, and in this case it is difficult to discriminate between monomer and inhibitor termination since the concentration of the inhibitor would be proportional to the monomer concentration. Then, with regard to the generation of activity, a great variety of methods exist such as the addition of free radicals, radiation, and substances such as peroxides and diazo-compounds which are now firmly believed to give rise to free radicals on thermal decomposition. There are therefore many systems still to be explored from this point of view, for the number of possible monomers is very large and the variety of catalysts very great. This general type of exploration must go on since it is only by the discovery of suitable ideal systems from the kinetic point of view that further analysis can be attempted.

The next stage in this kind of work is to seek for some further fundamental measurements, since the primary aim of the experiments is to establish a relationship between the structure

of the monomer and its ability to polymerise, this ability being expressed numerically as a bimolecular velocity coefficient. Before this can even be contemplated, the following matters have to be settled. (1) The velocity coefficients for the bimolecular growth reaction have to be determined as a function of size and of temperature, so that the energy of activation and the steric factors may be computed. (2) It has to be established whether or not the activity can be transferred to molecules of monomer thereby initiating the growth of another molecule of polymer, the original molecule of polymer losing its activity. (3) The magnitude of the velocity coefficient for the cessation of growth must likewise be determined as a function of molecular size and of temperature. It is also necessary to gain some idea of the nature of the products in this reaction. (4) The exact rate of the initiation process must be determined. (5) The precise nature of the active polymer or polymers, for there may be more than one variety, must be determined. (6) The distribution of molecular weights about the mean value must be known. These factors are enumerated on the assumptions that a reliable method exists for the determination of the number average molecular weight of the polymer, that the molecules are linear, and that means of efficient fractionation of the heterodisperse samples exist.

Exploratory investigations have revealed a system in which precise numerical answers to the above-enumerated questions may be obtained. This is the photopolymerisation of liquid vinyl acetate, which readily occurs with radiation at about 2500 A., with the production of linear polymers (for preliminary results, see Burnett and Melville, *Nature*, 1945, **156**, 661). No matter whether the polymerisation takes place in the gas phase, in the pure monomer, or in a solution of the polymer in an inert solvent, there is a very simple mathematical relationship defining the average rate of polymerisation, *viz.*,

$$\text{Rate} = k_p[\text{M}]I^{\frac{1}{2}}/k_t^{\frac{1}{2}}$$

where k_p is the average value of the bimolecular velocity coefficient for the interaction of active polymer with monomer, [M] is the monomer concentration, I the rate at which activity is induced in the monomer, and k_t the bimolecular coefficient for the reaction of the active polymer molecules leading to their destruction. There is also another simple expression, *viz.*,

$$\text{Rate} = k_p[\text{P}][\text{M}] = k_p I\tau[\text{M}]$$

where [P] is the total concentration of active polymer, which is numerically equal to its rate of production multiplied by its mean life τ to a close approximation.

The determination of I is not easy for the following reasons. Suppose polymerisation is initiated by the decomposition of a peroxide; then it is possible to measure the rate of decomposition of the peroxide in the monomer, and from this rate we might infer that two radicals each capable of initiating growth would be produced, *e.g.*,

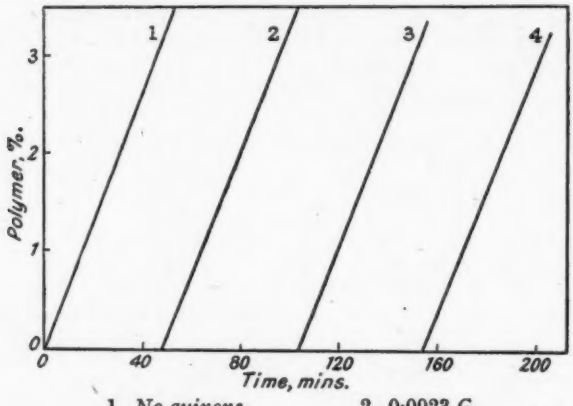
$$(C_6H_5{\cdot}CO{\cdot}O)_2 = C_6H_5 + C_6H_5{\cdot}CO{\cdot}O + CO_2$$

The difficulty here is to determine whether each radical so produced will, in fact, start a chain. To overcome this difficulty, some experimenters have introduced bromine atoms into the benzene ring of benzoyl peroxide and in that way have established qualitatively that the peroxide fragments enter the polymer molecule, thus enabling one to obtain the number average molecular weight of the polymer if no transfer occurs. In the gas phase, methyl radicals from photochemically decomposed acetone may likewise be employed. Acetone primarily decomposes into CH_3 and $CH_3{\cdot}CO$ and there is evidence that the $CH_3{\cdot}CO$ radical may be incorporated in the resultant polymer. At present, it would be true to say that all known catalytic substances react chemically with the monomer and thus become incorporated in the resulting polymer. There is no well-authenticated case where the catalyst induces physical activation of the double bond in the initial step in polymerisation. (It may be in some polymerisation reactions, for example, the thermal polymerisation of styrene, that primary activation in a bimolecular reaction between two monomers results in the production of an active polymer.) Therefore, in principle, by extension of these techniques, there is no barrier to our obtaining precise values of the rate of initiation.

When using radiation, which is particularly convenient in other respects, matters become much more complicated. There are three possibilities: (*a*) the electrons of the double bond are raised to a higher energy level, thus giving rise to an activated monomer molecule; (*b*) a diradical is formed by the opening of the double bond, though this may be an extreme case of (*a*); (*c*) the molecule may be dissociated into fragments which themselves may be free radicals. We cannot, unfortunately, assume that each quantum of radiation activates a molecule in one or other of these modes. However, it may be noted that mechanisms (*b*) and (*c*) give rise to a

free-radical growth, while (*a*) is of a completely different type, and a discrimination may be possible. Once more we must devise some specifically chemical method of detecting the number of molecules activated. This can be done by the judicious use of inhibitors. Fig. 1 shows the kind of inhibition obtained in the photopolymerisation of liquid vinyl acetate, which behaves ideally in the kinetic sense of the term. With pure vinyl acetate the plot of percentage polymerisation as a function of time is accurately linear over a considerable range. This reaction is of zero order. If a small amount of benzoquinone is added, a well-defined induction period appears, but thereafter the rate is precisely identical with that of the uninhibited reaction. Simultaneously, the faint colour of the quinone is destroyed. The induction period is accurately proportional to the amount of quinone added, and consequently we infer that each molecule of vinyl acetate photochemically activated reacts chemically with one molecule of quinone. The rate of removal of quinone therefore measures the rate at which vinyl acetate molecules are

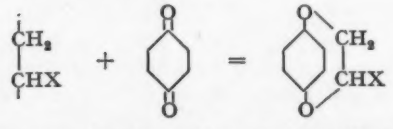
FIG. 1.



1. *No quinone.* 2. 0·0023 *G.*
3. 0·0050 *G.* 4. 0·0075 *G.*

Inhibition of photopolymerisation of vinyl acetate by benzoquinone.

activated. The precise chemistry of this reaction is not known, but it is easy to assume that a cyclic molecule might be formed in the following way:

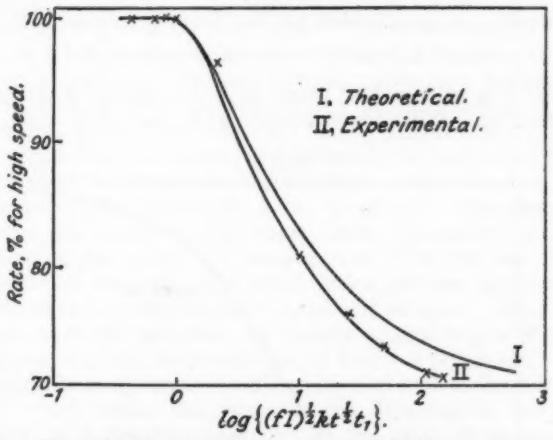


a scheme which would presuppose the formation of a diradical. The only assumption then made is that every molecule of acetate so activated can actually react with another ordinary molecule of acetate. This is so reasonable an assumption that it is unlikely to be wrong. In this particular case, it turns out that each quantum of radiation is effective in removing exactly one molecule of benzoquinone and therefore in activating one molecule of vinyl acetate. It is also noteworthy that one molecule of polymer is produced for each quantum absorbed. There is no question of the quinone becoming photoexcited and removing a molecule of vinyl acetate, for the extinction coefficient of the acetate is much greater than that of the quinone.

The next important problem is to determine the lifetime of the active polymer. This can only be done by utilising photochemical excitation, and therefore it renders photochemical methods particularly useful in dealing with this problem. Photochemical polymerisations are almost unique in that in a few cases, *e.g.*, methyl methacrylate and chloroprene, reaction may continue in the dark for minutes, hours, or even days after the light is switched off. In other cases, reaction is finished in a few milliseconds. The former type is extraordinarily difficult to investigate though it is of paramount interest, but unfortunately not much progress has been made towards elucidating the nature of this long-continued activity. This behaviour is not exhibited by vinyl acetate. The second class is more amenable to analysis. Here we have to measure the lifetime, *i.e.*, the time required for the polymer to grow to a specified size. This can

be done in two ways: If intermittent radiation is used to irradiate the system, it is found experimentally that the rate of polymerisation depends on the frequency of flashing. Fig. 2 shows the kind of behaviour observed. An accurate mathematical analysis of the shape of the rate–frequency curve enables one to compute the mean life of the active polymer when there is steady illumination. To show the sort of agreement obtained, it is predicted theoretically that the ratio of extreme rates should be 0·707 : 1, which is what is found. The theoretically calculated curve will be seen to lie very close to the experimental curve. Values of the lifetime to within a few % may readily be obtained by this method. The flashing technique may be applied to liquid and gas-phase reactions. Another method is applicable in the gas phase. If two parallel beams of light are projected into a reaction vessel, and if means are provided for varying the distance between the beams, then the velocity of polymerisation is a function of the distance because the chain started in one beam interferes with the chain started by the other beam (Jones and Melville, *Proc. Roy. Soc.*, 1940, *A*, **175**, 392). An estimate of the time of diffusion of such molecules may be made, and consequently the mean life may be computed. Owing to optical difficulties, such a method is not nearly so accurate as the flashing technique.

FIG. 2.



Rate of polymerisation–frequency of flashing curve.

The determination of the I and the τ together with the rate of polymerisation under defined conditions, thus enables the all-important quantity k_p to be calculated. The first question therefore is: how does k_p vary with molecular size? As the molecule grows, does the monomer find it more and more difficult to locate and to add on to the active end of the growing polymer? If it does, what is due to an increase in activation energy and what is due to a change in the temperature-independent factor of the bimolecular coefficient? So far, exact measurements have only been made for vinyl acetate polymers and the following typical results obtained:

Chain length	174	339
k_p, l. mols.$^{-1}$ sec.$^{-1}$	$7{\cdot}7 \times 10^2$	$6{\cdot}7 \times 10^2$

It will be seen that k_p only decreases very slightly when the molecular weight is doubled. Measurements have not yet been extended to low chain lengths owing to technical difficulties, but it is quite possible that there may be a greater variation during the early stages of growth. The temperature coefficient of k_p shows that the energy of activation for growth is 4·4 kcals. Values of this order have often been mentioned, but this is the first exact and unambiguous value for any reaction. This low value naturally accounts for the rapidity of polymer growth. The temperature-independent factor, 10^{-6}, is much lower than the normal value, thus implying that in every collision where energy of activation is present reaction does not necessarily occur. This is not surprising in view of the fact that a small molecule has to react with a relatively small spot in a large molecule, and it is not certain in what shape the polymer molecule exists in solution. The determination of k_p, in turn, enables the magnitude of the k_t to be calculated. All the data are available and we need only quote the following results:

Chain length	174	340
k_t, l. mols.$^{-1}$ sec.$^{-1}$	$3{\cdot}1 \times 10^9$	$2{\cdot}5 \times 10^9$

The remarkable result is that k_t only decreases very slightly with increased molecular weight. Further, k_t is unaffected by temperature; therefore no activation energy is necessary for the interaction of the active polymers. Curiously enough, the steric factor is quite large, about 10^{-2}, so it would appear that the active ends of the polymer have no special difficulty in colliding and in interacting.

Though the evidence is not yet absolutely conclusive quantitatively, there are very strong grounds for believing that the active polymer in this case is a very large diradical. It is most unlikely that polymerisation would cease by interaction of the two ends of such a radical to produce a large cyclic molecule. On the other hand, it is equally unlikely that termination of growth would occur by the combination of the end of these radicals with each other, for then extremely long molecules would be produced and such a process would not result in complete destruction of activity. On the other hand, a disproportionation reaction between the ends of the active polymer, if it did occur, would mean that each diradical initially produced would ultimately form an inactive polymer, thus:

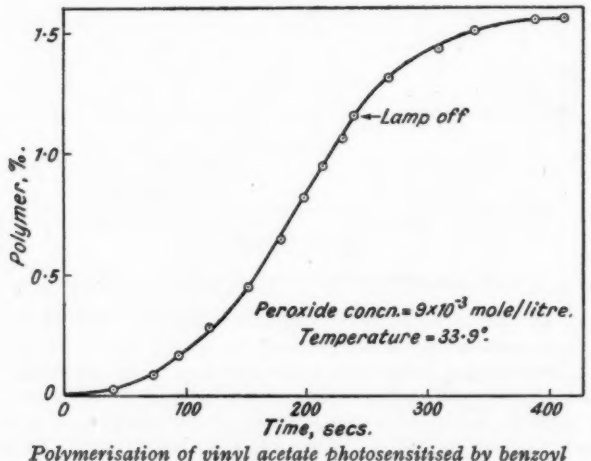
$$\begin{array}{ll} R{-}CH_2{-}CHX{-} & {-}CHX{-}CH_2{-}R \\ R{-}CH_2{-}CH_2X & HCX{=}CH{-}R \end{array}$$

This matter may, however, be complicated by the transfer reaction of the following type:

$$R + CH_2{=}CHX \longrightarrow R{-}H + {-}CH{=}CHX$$

In this particular event, it is evident that many polymer molecules will be produced for each monomer initially activated. With vinyl acetate this does not occur, for each quantum

FIG. 3.



Polymerisation of vinyl acetate photosensitised by benzoyl peroxide.

absorbed produces only one polymer molecule and not several such molecules. Further, each molecule of polymer corresponds exactly to one molecule of monomer initially photoactivated, and hence there is no question that the diradicals undergo disproportionation. Therefore, by a combination of the measurements of number average molecular weights and the number of monomers initially activated, it is immediately possible to detect the existence of transfer, and of other types of reaction peculiar to polymer kinetics.

As has already been mentioned, it is now believed that many vinyl polymerisations proceed by the free-radical mechanism, but because there appear to exist other mechanisms whose nature is not yet established, it is absolutely essential to prove that, in a given reaction, free radicals are actually involved. Again, considering vinyl acetate, the matter can be settled in this way. With methyl methacrylate and styrene it can be shown that free radicals of the triphenylmethyl type initiate polymerisation, giving rates and molecular weights which are comparable with those obtained by the use of peroxides. A considerable amount of quite independent evidence shows that peroxides decompose thermally to free radicals; therefore it seems an inescapable conclusion that peroxide-induced polymerisation occurs by the free-radical mechanism. Similarly, it has recently been found that peroxides may be decomposed

photochemically, and that photodecomposition in the presence of vinyl monomers gives rise to polymerisation having similar characteristics to the direct photochemical reaction on the one hand and to the thermal benzoyl peroxide-catalysed reaction on the other. The study of the benzoyl peroxide-photosensitised reaction is of particular interest in another connexion in addition to providing the connecting link in support of the free-radical mechanism. Fig. 3 shows the relationship between amount of polymer formed and time. There is a well-marked induction period, and when the light is switched off the reaction continues in the dark. No such behaviour is obtained in the direct photoreaction. The dark-rate curve is, however, precisely the reverse of the induction-period curve. But the induction period is not due to the presence of inhibitors, and the dark rate is not due to polymer molecules where activity persists in the dark. The whole phenomenon is due to the fact that the radicals, phenyl and benzoate, from the benzoyl peroxide do not immediately react with vinyl acetate, and that it takes quite a time to build up a stationary concentration of such radicals. Similarly, when the light is switched off the concentration of the radicals decreases slowly, fewer and fewer vinyl acetate chains being started. By an analysis of the induction-period and dark-rate curves it is possible to measure the magnitude of the bimolecular coefficient for the reaction of a free radical from benzoyl peroxide with vinyl acetate. This may be done at different temperatures, and hence the energy of activation and steric factor evaluated. These are 8·5 kcals. and 10^{-6}, respectively. It is surprising that vinyl acetate molecules can add on to a free radical of polyvinyl acetate much more readily than a phenyl or benzoate radical. Therefore, the general conclusion must be that, when such an initial process is involved in a polymerisation, it may be necessary to correct for the relative inactivity of radicals even in the presence of fairly reactive monomers. These observations thus provide a connecting link between the photo- and the peroxide-catalysed reactions and show them to be identical in mechanism. We therefore conclude that, when radiation activates vinyl acetate, a diradical is in fact produced. This is not a general conclusion, for it may be mentioned that in the vapour phase, with, *e.g.*, methyl vinyl ketone (Jones and Melville, *Proc. Roy. Soc.*, in the press), the behaviour is quite different, since this molecule is decomposed into free radicals and only the methyl radical initiates polymerisation.

The final matter relates to the distribution of molecular weights. Since all kinetic coefficients relating to the reaction are known and since no transfer occurs, it is theoretically possible to set down equations describing the rate of production of inactive polymers. If there is no simple mathematical relationship between the velocity coefficient and molecular size, it is difficult to solve these equations which define the shape of the distribution curve. To a very close approximation, however, it is possible to state that the ratio of propagation to termination coefficients is practically independent of molecular size, and hence the precise shape of the weight-distribution curve can be computed, and previous calculations confirmed. The real difficulty here is to fractionate the polymer sufficiently well to see whether the observed distribution agrees with the theoretical curve. It is easy by the usual fractional procedure to show that the general shape is all right but its precise shape cannot so easily be determined. There is in fact an urgent need for a fractionation method of some automatic kind to give really good fractionation, for this method would be invaluable in producing additional evidence in support of conclusions arrived at by kinetic methods alone.

These notes may have shown how much further kinetic analysis may be pushed when ideal enough systems can be found. There is by no means finality in this phase, for many fundamental problems have still to be tackled. Structurally, there are many stereoisomers in even simple vinyl polymers. At present there is no knowledge how reaction conditions affect structural detail. There is very little evidence to show whether environment affects velocity coefficient. Many polymers may be branched or even cross-linked, thus complicating kinetic experiments. There is no reliable information regarding the nature of the processes that give rise to chain branching. There are mechanisms leading to the formation of polymers that do not involve radicals at all, and their nature has not yet been determined nor have the kinetics been investigated in detail.

Discussion.

DR. G. B. B. M. SUTHERLAND: I should like to ask Professor Melville whether he has considered the possibility of applying spectroscopic methods to the detection and estimation of the free radicals assumed present in polymerisation of vinyl compounds? It may be that the concentrations present or the life times are impossibly small, but it would be interesting to have the precise figures.

MR. W. COOPER: The rates of reaction of oxidation–reduction polymerisations are very fast,

and the molecular weights of the products very high (B.PP. 573,366, 573,369). This leads to the suggestion that the principal influence of the reducing agent is on the mechanism of the termination reactions. Molecular oxygen, because of its unpaired electrons, can terminate growing chains (in the same way as mesomeric free radicals and inhibitors which can form semi-quinonoid free radicals; Waters, *Trans. Faraday Soc.*, 1941, **37**, 774). The ferrous reducing agent, by removing any free oxygen present and suppressing its formation from the oxidising catalyst, together with the free hydroxyl radicals of high activity formed, would produce a rapid reaction rate with formation of high polymers.

MR. J. H. BAXENDALE: From the observation that each quantum absorbed in the initiating reaction leads to one polymer molecule, Melville concludes that the terminating reaction in vinyl acetate polymerisation is a disproportionation, *viz.*,

$$—CH_2—+ —CH_2—CHX— \longrightarrow —CH_3 + CH_2{=}CX—$$

However, the observed values of the velocity constant for this reaction show that it has no activation energy. It would seem unlikely that a reaction involving an atom transfer will go without activation energy, and for a reaction such as

$$H + CH_4 \longrightarrow CH_3— + H_2$$

it is found to be about 10 kcals. (Steacie, *Chem. Reviews*, 1938, **22**, 333). We should expect a value of this order (probably somewhat smaller because of the greater exothermicity) for the disproportionation. It would appear more probable that termination occurs by mutual combination of two growing polymer chains, which is apparently the case for aqueous solution polymerisation, and which requires little or no activation energy. However, such a mechanism would mean that each polymer molecule originates from two initiating radicals produced by the radiation, compared with one in the case of disproportionation. Since each quantum yields one polymer molecule, a mutual termination mechanism would imply that the photochemical initiation reaction produces two separate atoms or free radicals per quantum, instead of the proposed diradical.

PROF. H. W. MELVILLE: In reply to Dr. Sutherland's question I would say that very unfortunately the method is unlikely to be sufficiently sensitive since the concentration of the free radicals is only 10^{-8} mole/litre whereas the concentration of monomer is 10 moles/litre. Unless the radicals possessed a very high extinction coefficient indeed it would be difficult to detect their presence. Even magnetic measurements are not sensitive enough for this purpose.

Mr. Cooper's suggestion that the reducing agent in oxidation–reduction polymerisation affects the course of termination reaction is not supported by what kinetic evidence is available. Even in aqueous systems interaction of two radicals is usually the determining factor. The reason for the high velocities and high molecular weights at low temperatures is most probably the so-called "gel" effect in which the value of the termination velocity coefficient is diminished because the active free-radical ends of the polymer cannot easily meet owing to the fact that the polymer is precipitated out of the system in the act of growing.

Mr. Baxendale's suggestion that monoradicals rather than diradicals take part in the polymerisation is of course a possibility provided the two free radicals combine in the termination reaction. The facts are that one polymer molecule is produced for each quantum absorbed, and there is no evidence that the molecule of vinyl acetate is dissociated. In fact experiments with the vapour have shown clearly that the vinyl acetate molecule is activated electronically and can lose its energy by collision with helium and argon atoms. The best evidence, however, comes from the action of inhibitors. Although benzoquinone gives rise to a well-marked induction period in the direct photo-reaction, yet, when the reaction is initiated by the decomposition of benzoyl peroxide, benzoquinone acts only as a retarder. This differentiation is common also to the polymerisation of styrene and of methyl methacrylate and seems to provide a general method for discriminating between diradicals and monoradicals.

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5. *Equilibrium Properties of High Polymer Solutions and Gels.*

By GEOFFREY GEE.

THE equilibrium between a polymer and liquid is of fundamental importance in a number of problems of considerable practical as well as theoretical interest. As examples may be mentioned: (1) the choice of a solvent or plasticiser for a given polymer, (2) choice of a suitable

polymer for use, *e.g.*, as a gasket in contact with specified liquids, (3) the combined solvent or swelling action of mixture of liquids, (4) the effect of mechanical deformation, *e.g.*, compression, on the solvent resistance of a polymer, (5) the separation of a polymer into fractions by the use of solvent-precipitant mixtures. It must be emphasised at the outset that in some of them other factors are involved; these will not be considered in the present paper. The basic assumption is made here that, given time, a system comprising polymer and liquid will reach a steady state, and that if two condensed phases are then present, they must be in true thermodynamic equilibrium. The disturbing influence of such time-dependent processes as degradation and plastic flow may in certain practical cases prevent the attainment of a steady state, but these possibilities require separate discussion. Within the limited space available, all that can be attempted is a brief outline of the general methods which have been used, illustrated by applying them to the first two of the above problems.

Thermodynamic Formulation of the Problem.—The function which will be used in discussing polymer–liquid equilibria is the Gibbs free energy of dilution of a polymer–liquid mixture by the pure liquid. It is denoted by ΔG_0 and defined as the increase in the Gibbs free energy G when 1 mole of liquid is transferred from a reservoir of pure liquid to an infinitely large bulk of a polymer–liquid mixture. Formally, if n_0 and n_r are the numbers of moles of liquid and of polymer in the mixture, at temperature T,

$$\Delta G_0 = \left(\frac{\partial G}{\partial n_0}\right)_{n_r,\,T} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Experimental measurements of ΔG_0 are based on observations of the vapour pressure p_0^m or other related properties of the mixture. If p_0^0 is the vapour pressure of the pure liquid, it may be shown (Gee and Treloar, *Trans. Faraday Soc.*, 1942, **38**, 147) that

$$\Delta G_0 = RT \ln (p_0^m/p_0^0) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The temperature dependence of ΔG_0 may be employed to calculate the heat ΔH_0 and entropy ΔS_0 of dilution; these are respectively the increases in heat content H and entropy S accompanying the transfer of liquid as defined above. Their relations to ΔG_0 are:

$$\Delta S_0 = (\partial \Delta G_0/\partial T)_{n_0,\,n_r} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\Delta H_0 = \Delta G_0 + T\Delta S_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The condition for a polymer–liquid mixture to be in equilibrium with excess of liquid is simply $\Delta G_0 = 0$. If a swollen polymer is placed in contact with excess of liquid, further absorption of liquid will occur so long as the Gibbs free energy of the system is thereby decreased (ΔG_0 negative). If this is true at all concentrations of the mixture, the polymer and liquid in question will be miscible in all proportions. It is clear, therefore, that if some general expression could be found, giving ΔG_0 as a function of the composition of a polymer–liquid mixture, then equating this function to zero would give at once the composition of the mixture which would be in equilibrium with excess liquid. The next section describes some of the attempts which have been made to deduce such an expression.

The discussion so far has neglected the dispersion and solution of polymers in the liquid. This is only strictly justified in the case of polymers which are completely cross linked into a network. Linear polymers have, in principle, a finite solubility in any liquid, and in order to define an equilibrium between polymer and liquid it is necessary to specify the relative volumes of the two phases and the amount of polymer present in each. There are then two equilibrium conditions to be observed; namely, that the Gibbs free energy of the system shall be unaffected by transfer of small amounts of either liquid or polymer from one phase to the other. In practice it is found that in almost all cases in which the polymer and liquid are not miscible in all proportions, the amount of polymer present in the liquid phase is so small that the liquid is virtually indistinguishable from pure liquid. The conditions under which two phases in equilibrium may both contain appreciable concentrations of polymer are so critical that they are encountered only when a range of molecular weights is present.

The extension of this formulation to systems containing more than one type of liquid is straightforward (Gee, *ibid.*, 1944, **40**, 463, 468), and will not be discussed in detail. The two important problems are (*a*) the swelling of an insoluble polymer in mixtures, and (*b*) the fractionation of soluble polymers. In the former, differential absorption of the two liquids generally occurs, and two equations are required to define the complete composition of the swollen polymers at equilibrium. These are obtained from the conditions that the Gibbs free energy of the system must be unaffected by small transfers of either liquid from one phase to the other. The problem of fractionation is very complicated; even if the distribution of molecular

weights is represented by a mixture of two only, there are four components distributed between the two phases, and therefore four conditions to be satisfied for equilibrium. These are readily written down but are too complex to be of any practical value in their complete form.

The Statistical Approach to the Problem.—It has been shown above by thermodynamic reasoning that the problem of the equilibrium between a polymer and a liquid would be solved if an expression could be found for the dependence of the free energy of dilution on composition and temperature. The deduction of such an expression in terms of molecular properties of the polymer and liquid is a problem in statistical mechanics, and several attempts have been made to solve it (Flory, *J. Chem. Physics*, 1941, **9**, 660; 1942, **10**, 51; Huggins, *ibid.*, 1941, **9**, 440; *Ann. N.Y. Acad. Sci.*, 1942, **43**, 1; *J. Physical Chem.*, 1942, **46**, 1; *Ind. Eng. Chem.*, 1943, **35**, 216; Miller, *Proc. Camb. Phil. Soc.*, 1942, **38**, 109; 1943, **39**, 54, 131; Guggenheim, *Proc. Roy. Soc.*, 1944, *A*, **183**, 203, 213; *Trans. Faraday Soc.*, 1945, **41**, 107; Orr, *ibid.*, 1944, **40**, 306, 320). The detailed description of these attempts is outside the scope of the present paper, and reference will be made only to the basic assumptions and the final results. To a first approximation the calculation of ΔG_0 may be reduced to the two independent problems of finding expressions for ΔS_0 and ΔH_0. This approximation is valid if the mixing of polymer and liquid occurs in a completely random way.

Statistical derivations of ΔS_0 depend on Boltzmann's equation relating the entropy S of a state to its thermodynamic probability W

$$S = k \ln W \qquad (5)$$

where k is Boltzmann's constant. Considering an assembly of polymer molecules and liquid molecules, if W_1, W_2, and W_3 are the respective probabilities of the polymer molecules alone, the liquid molecules alone, and a random mixture, then by equation (5) the increase of entropy ΔS^m consequent upon mixing the components is given by

$$\Delta S^m = k \ln \left(\frac{W_3}{W_1 W_2} \right) \qquad (6)$$

By analogy with equation (1), ΔS_0 is then defined as $(\partial \Delta S^m / \partial n_0)_{n_r, T}$. In order to compute the probabilities it is necessary to have a definite molecular model of the assembly; the one which has been used divides the space occupied by the assembly into a series of sites arranged in a regular lattice formation, defined by a fixed co-ordination number Z (*i.e.*, the number of nearest neighbours of any selected site). Each site is assumed to be capable of holding a single molecule of the liquid, and the spacing of the sites fixed by the known density of the liquid, "holes" being neglected. It is then imagined that the polymer can be divided into sections, each having the same volume as a molecule of liquid, and therefore capable of occupying a single site. The flexibility of the polymer is taken into account by supposing that a molecule of polymer can be arranged on any set of sites subject only to the restriction that adjacent sections of the polymer chain must occupy adjacent sites. The thermodynamic probability of the assembly is then obtained by computing the number of ways of arranging it on the lattice. In this way an expression will be obtained for ΔS_0 in terms of the composition of the mixture, the number of sites (x) occupied by a single molecule of polymer, and the co-ordination number Z. It is clear from the description of the model that x is equal to the ratio between the molecular volumes of the polymer and liquid, and that the natural unit of composition is the volume fraction v_r of polymer, *i.e.*, the fraction of the total volume occupied by polymer.

The enumeration of the configurations of a polymer presents difficulties, arising from the necessity to exclude impossible arrangements in which two sections of a chain occupy the same site. Considering the process of adding a polymer molecule, section by section, to a partly filled lattice, the difficulty arises in estimating the probable number of sites available for the i'th section. The $(i-1)$'th section is supposed to be in place; of its Z neighbouring sites one must be occupied by the $(i-2)$'th section, but the probable number of the remaining $(Z-1)$ which are vacant will clearly depend both on i and on the fraction of the total space which has already been filled. Flory (*loc. cit.*) neglected the dependence on i, and obtained the final result in a remarkably simple form:

$$\Delta S_0 = -R\{\ln (1 - v_r) + v_r (1 - 1/x)\} \qquad (7)$$

ΔS_0 is seen to be independent of Z, while the dependence on x is only important when v_r is small enough to be comparable with $1/x$. Huggins (*loc. cit.*) attempted a partial correction for the dependence on i, and obtained finally

$$\Delta S_0 = -R\left\{ \ln (1 - v_r) - \tfrac{1}{2} Z' (1 - 1/x) \ln \left(1 - \frac{2 v_r}{Z'} \right) \right\} \qquad (8)$$

where Z' is nearly identical with Z. Miller (*loc. cit.*), by a different method of computation which will not be described here, obtained the very similar result

$$\Delta S_0 = -R\left[\ln(1-v_r) - \tfrac{1}{2}Z\ln\left\{1-\frac{2v_r}{Z}(1-1/x)\right\}\right] \quad . \quad . \quad . \quad . \quad . \quad (9)$$

It will be seen that Flory's result is identical with the asymptotic limit of (8) or (9) for large values of Z.

The heat of dilution has its origin in the exchange of partners between polymer and liquid during mixing. The transfer of a molecule of liquid from liquid to polymer may be imagined to take place in three steps, involving (1) evaporation of a molecule of liquid, (2) separation of the polymer chains so as to form a hole into which (3) the molecule of liquid is condensed. The first two steps require an absorption of energy in overcoming the cohesive forces of the liquid and the polymer; in the third, energy is recovered, and the heat of dilution is the algebraic sum of the three. A complete theory should predict the form of dependence of ΔH_0 on composition, and relate its magnitude to those of the intermolecular forces. The problem is very similar to that of calculating the heat of dilution ΔH_1 of a mixture of two liquids (1 and 2) by liquid 1; this has been discussed by van Laar (*Z. physikal. Chem.*, 1928, *A*, **137**, 421), Hildebrand ("Solubility," Reinhold, N.Y., 1936), Scatchard (*Chem. Reviews*, 1931, **1**, 321), and others. For random mixing of liquids it is easily shown that ΔH_1 should be proportional to the square of the concentration of species 2, but it is not at once clear in what units the concentration should be expressed. If the number of contacts is taken to be the important factor, then concentrations should be in mole fractions; if the effective surface of contact is the determining factor, volume fractions will be more appropriate. Experimental evidence (Hildebrand, *op. cit.*) is strongly in favour of the latter, and in most treatments of polymer solutions, it has been assumed that the same relation would apply, *i.e.*,

$$\Delta H_0 = \alpha v_r^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

where α is a constant. Although this type of expression will be used below, it must be pointed out that it is not strictly consistent with the model used in calculating ΔS_0. This would relate the heat of dilution to the number of polymer–liquid contacts, and (10) should be replaced by

$$\Delta H_0 = \alpha'\left\{\frac{qv_r}{1+(q-1)v_r}\right\}^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where

$$q = 1 - \frac{2}{Z} - \frac{2}{xZ} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Equations (10) and (11) are only identical in form in the physically meaningless case of $Z = \infty$.

In order to complete the calculation of ΔH_0 it is necessary to find an expression for α (or α'), and the only suggestion which has been made (Gee, *Trans. Faraday Soc.*, 1942, **38**, 418) is to use the method applied by Hildebrand to liquid mixtures. The energy required to separate all the molecules in 1 c.c. of the liquid is the cohesive energy density of the liquid (E_{00}) given by

$$E_{00} = (L_0 - RT)/V_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

where L_0 is the molar latent heat of evaporation and V_0 the molar volume. Although equation (13) cannot be applied to the polymer, it is perfectly logical to speak of its cohesive energy E_{rr}, to be estimated as described below. It is still necessary to know how the energy of a polymer–liquid contact is related to those of liquid–liquid and polymer–polymer contacts. The assumption of a geometric mean is likely to be valid when the forces involved are purely dispersion forces, and leads to the result

$$\alpha = V_0(\sqrt{E_{00}} - \sqrt{E_{rr}})^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

Experimental evidence as to the usefulness of this relationship will be given in a later section.

The simplest equation which can be obtained for the free energy of dilution results from combining equations (4), (7), and (10), to give

$$\Delta G_0 = RT\left\{\ln(1-v_r) + v_r(1-1/x) + \frac{\alpha}{RT}v_r^2\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

If equation (8) or (9) were used in place of (7) the final result would be almost identical, except that α/RT would be replaced by

$$\mu = \mu_0 + \alpha/RT \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

where μ_0 is a function of Z but is nearly independent of v_r. This is the general form of the free-energy equation as deduced by the approximate method outlined. For convenience it may be written in two approximate forms

(*a*) for dilute solution,

$$-\Delta G_0 = RT\left\{\frac{v_r}{x} + (\tfrac{1}{2} - \mu)\, v_r^2\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

(*b*) at higher concentrations ($v_r > 0{\cdot}1$)

$$\Delta G_0 = RT\{\ln (1 - v_r) + v_r + \mu v_r^2\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

So far it has been assumed that the mixture is completely random, but it is clear that, unless the heat of dilution is zero, some configurations will be energetically favoured, and should accordingly be weighted in computing the configurations of the system. This has been done in different ways by Orr and by Guggenheim (*locc. cit.*), but the detailed results will not be quoted. The general conclusion is that a positive heat of dilution ($\Delta H_0 > 0$) results in non-random mixing which increases ΔS_0 at low v_r and decreases it at high v_r. The effect, however, is very small, even when the heat of dilution is large, and seems unlikely to be important compared with the assumptions and approximations inherent in the method.

All methods of calculation used hitherto break down seriously for solutions sufficiently dilute for the polymer molecules to be individually dispersed, with relatively little overlap. In this region it is evident that, although the fraction of sites occupied by polymer is small, there will be a relatively high probability of finding an occupied site adjacent to any selected site known to be occupied. In other words, the assembly may more properly be thought of as a dispersion of regions of fairly high concentration in a medium which elsewhere is pure liquid. This conclusion may be put in another way by saying that in an infinitely dilute solution there will still be a fairly large number of points at which sections of a polymer chain occupy adjacent sites. According to the method of calculation described above, in an infinitely dilute solution there would be no polymer–polymer contacts. The present theory of dilute solutions is therefore definitely wrong, and two attempts to provide a new treatment may be mentioned. (*a*) Orr (*Trans. Faraday Soc.*, in the press) has considered the arrangement of a single chain on a lattice, and has made tentative estimates of the number of polymer–polymer contacts to be expected, as a function of the heat of mixing. (*b*) Flory (*J. Chem. Physics*, 1945, **13**, 453) has used the experimentally observed viscosity to make a rough estimate of the number of sites enclosed within the " envelope " of a single polymer molecule which, in the examples he quotes, is of the order of $50x$. On this basis he has estimated that the quadratic term in the expansion for ΔS_0 may be several times smaller than that given by equation (17). There is no doubt of the reality of this discrepancy, but its quantitative treatment by purely statistical methods has not yet been accomplished.

One other factor which must be mentioned is the effect of cross linking of the polymer. So far the polymer has been assumed linear, and it is clear that the introduction of cross links between different polymer chains will reduce the number of configurations of the system, and therefore diminish ΔS_0. It is not proposed to describe here how this effect on ΔS_0 has been calculated; the result obtained (Flory and Rehner, *ibid.*, 1943, **11**, 521) is

$$\Delta S_0 = -\frac{R\rho_r V_0}{M_e} v_r^{-\frac{1}{3}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

where ρ_r is the density of the polymer, and M_e the " molecular weight " of the portion of the polymer between adjacent junction points. The free energy of dilution of a cross-linked polymer is therefore given by

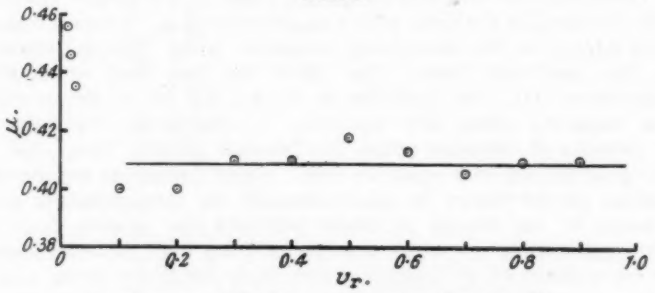
$$\Delta G_0 = RT\left\{\ln (1 - v_r) + v_r + \mu v_r^2 + \frac{\rho_r V_0}{M_e} v_r^{-\frac{1}{3}}\right\} \quad . \quad . \quad . \quad . \quad . \quad (20)$$

The last term is always positive and tends to infinity as $v_r \longrightarrow 0$; it therefore gives a formal representation of the fact that the amount of any liquid which can be imbibed by a cross-linked polymer is finite.

Experimental Determination of the Free Energy of Dilution.—The theory outlined in the previous section leads to the conclusion that the driving force responsible for the imbibition of liquids by polymers is the large increase of entropy thereby produced; this increase has been estimated quantitatively. The controlling factor in determining the free energy of dilution in various systems is, on this view, the heat of dilution, and the form and approximate magnitude of this have also been estimated. There is at present a great lack of precise data by which these conclusions may be tested. Rough vapour-pressure data for a number of polymer–liquid

systems give reasonably accurate values of ΔG_0 [by equation (2)] but in very few cases is even the sign of the heat of dilution known with certainty. There is, however, abundant evidence that aqueous systems in general are not covered by the theory as developed, since for these ΔH_0 and ΔS_0 are both usually negative (Katz, *Ergeb. exakt. Naturwiss.*, 1924, **3**, 316; Urquhart and Williams, *J. Text. Inst.*, 1924, **15**, 559; Fricke and Lüke, *Z. Elektrochem.*, 1930, **36**, 309). This discrepancy undoubtedly arises from the attachment of the water molecules to the polymer

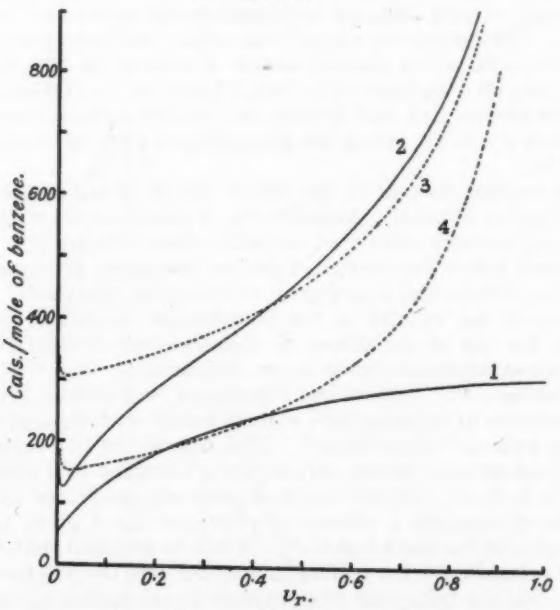
FIG. 1.



Free energy of dilution : natural rubber + benzene.

$$\mu = \frac{1}{v_r^2}\left\{\frac{\Delta G_0}{RT} - \ln(1-v_r) - v_r\left(1-\frac{1}{x}\right)\right\}.$$

FIG. 2.



Thermodynamic data for natural rubber and benzene.

Curve 1 : $\Delta H_0/v_r^2$. *Curve* 3 : $T\Delta S_0/v_r^2$, *theoretical* ($z = \infty$
Curve 2 : $T\Delta S_0/v_r^2$. *Curve* 4 : $T\Delta S_0/v_r^2$, *theoretical* ($z = 4$).

by hydrogen bonds, thus giving the swollen polymer a relatively high degree of order. It is clear that effects of this nature become increasingly probable as the system considered becomes more polar, and that the theory which has been developed can only be expected to hold for relatively non-polar materials. In the following discussion, aqueous systems will therefore be ignored. It must also be pointed out that volume changes accompanying swelling have been implicitly neglected. Where these occur they will make quite large contributions to both the heat and the entropy of dilution, but always in the same direction, leaving the free energy approximately that to be expected if the volume had remained constant. Thus, *e.g.*, the

swelling of natural rubber in *n*-pentane is accompanied by a considerable contraction, and in consequence both ΔH_0 and ΔS_0 must be much lower than would otherwise have been the case (Gee, unpublished).

By far the most complete data available are those for natural rubber and benzene, which cover practically the whole range of composition at different temperatures (Gee and Treloar, *loc. cit.*; Gee and Orr, *Trans. Faraday Soc.*, 1946, **42**, 507). The free energy of dilution is therefore known accurately from $v_r = 0{\cdot}005$ to $0{\cdot}999$, and the heat and entropy of dilution approximately. The results are summarised in Figs. 1 and 2; the former shows how accurately equations (17) and (18) describe the data, with a single value of μ. Despite this striking success, Fig. 2 reveals that $\Delta H_0/v_r^2$ is far from being constant, while $T\Delta S_0/v_r^2$ shows corresponding deviations from the predicted form. The data for the heat of dilution cannot be represented by equation (11), the dependence of $\Delta H_0/v_r^2$ on v_r being different in form from that to be expected from this equation. Furthermore, the heat of dilution of squalene, which contains 6 isoprene units, by benzene (Ferry, Gee, and Treloar, *ibid.*, 1945, **41**, 340) is in good accord with equation (10). These deviations are therefore believed to arise from the failure of the theory to allow correctly for intramolecular polymer–polymer contacts. This defect in the theory of dilute solutions has already been discussed; the experimental data suggest that the effect extends to quite high concentrations. It is found that the data can be understood by supposing that in an infinitely dilute solution of natural rubber in benzene some 23% of the contacts made by sections of the rubber chain are intramolecular. The constancy of μ means that the low heat of dilution is balanced by a correspondingly low entropy of dilution, leaving ΔG_0 almost equal to the theoretical value.

Data for other polymer–liquid systems are for the most part confined to a single temperature, or of insufficient accuracy to justify the calculation of ΔS_0 from equation (3). Huggins (*loc. cit.*) has shown that the bulk of such data can be satisfactorily represented by equations (17) and (18) with constant μ. The results for non-solvents which are very poor swelling agents show small deviations. For instance, for natural rubber + acetone at 35° Lens's data (*Rec. Trav. chim.*, 1932, **51**, 971) require a variation of μ from 1·5 at $v_r = 1$ to 1·3 at $v_r = 0{\cdot}75$ (the limit of imbibition). Similarly (Ferry, Gee, and Treloar, *loc. cit.*), for natural rubber + methyl alcohol at 30° μ diminishes from 4·7 to 3·6 during the absorption of 2·5% of alcohol, while $\Delta H_0/v_r^2$ falls by a factor of at least 10.

Perhaps the most striking success of the theory lies in giving so accurately the absolute magnitude of the entropy of dilution. Although Fig. 2 reveals errors in the form of the ΔS_0–v_r curve, it shows that ΔS_0 has been calculated correctly within a factor of 2. When it is recalled that the theories current before the modern statistical treatment gave values of ΔS_0 too small by a factor of 1000, it is evident that a very great advance has been made.

These limited tests of the validity of the fundamental statistical results are sufficiently successful to warrant the use of the theory in discussing equilibrium properties of polymer solutions and gels; two examples are given in the next section.

(a) *Oil-resisting Rubbers.* (b) *Solvents and Plasticisers for Polymers.*—The greater resistance of certain synthetic rubbers to hydrocarbons such as petrol, as compared with natural rubber, has led to their being termed "oil-resisting". This description is a complete misnomer, since these rubbers differ from natural rubber only in being resistant to a different class of liquid. The general problem is to find a polymer which is relatively unaffected by a specified liquid or liquids. The problem of selecting a solvent or plasticiser for a given polymer is the exact converse and the two can be discussed together. It will be assumed that a plasticiser is simply a liquid of low vapour pressure which is readily compatible with the polymer.

It has been shown that the behaviour of a polymer–liquid system can be characterised by a single constant μ. Now the thermodynamic condition for a polymer to be resistant to a liquid is that ΔG_0 shall be zero at a fairly large value of v_r. Inspection of equation (18) shows that this will be the case when μ is large; the controlling effect of μ is illustrated by Fig. 3 in which $\Delta G_0/Tv_r^2$ is plotted against the degree of swelling Q $(= 1/v_r - 1)$ for various values of μ. If μ is small, the liquid is a solvent or a good swelling agent; as μ increases, the maximum swelling decreases rapidly. It is clear, therefore, that in order to be able to choose a plasticiser for a given polymer, or a polymer to be used in contact with a specified liquid, it is necessary to find what physical properties of the polymer and liquid determine the magnitude of μ. Equations (14) and (16) give the basis of the answer to this problem; combining them, we have

$$\mu = \mu_0 + \frac{V_0}{RT}(\sqrt{E_{00}} - \sqrt{E_{rr}})^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

μ_0 will in general be small ($< 0{\cdot}5$), so that the magnitude of μ will be determined essentially by the difference between the cohesive energy densities of the liquid and the polymer. Equation

FIG. 3.

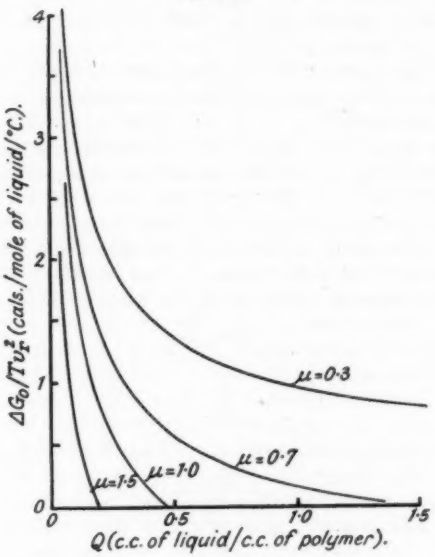
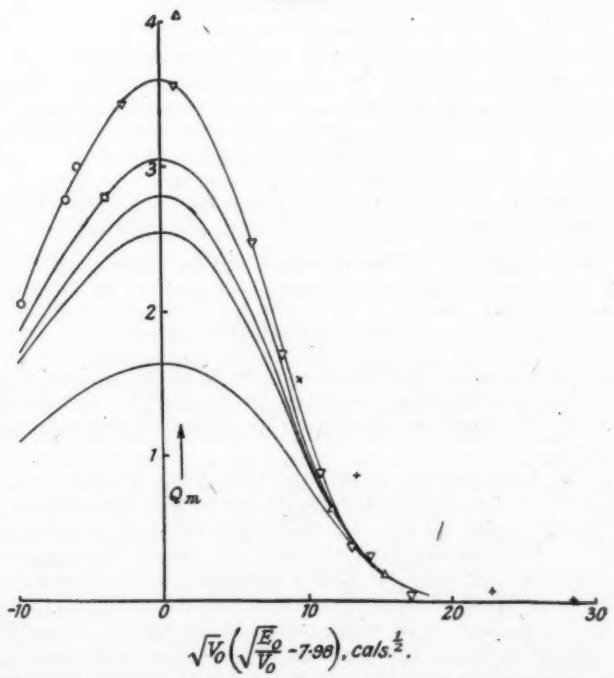


FIG. 4.

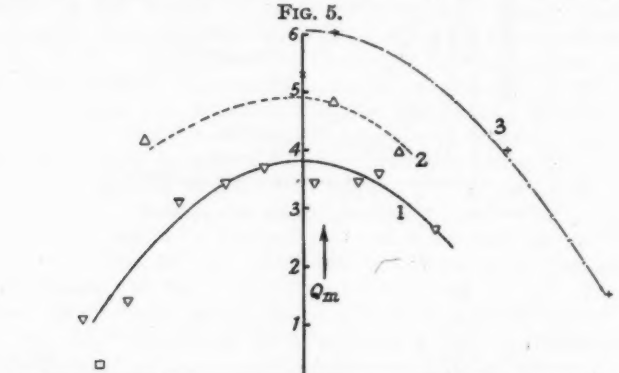


Swelling of five natural rubber vulcanisates in a range of aliphatic liquids.
Points (top curve only) : ○ *Hydrocarbons,* □ *Ethers,* ▽ *Esters,* △ *Ketones,* × *Aldehydes,* + *Nitriles.*

(21) is not found to be quantitatively valid; values of μ calculated by its aid are generally too small, but it has been used with considerable success in the following qualitative manner. Consider the swelling or solution of a given polymer in a range of liquids, arranged in order of

increasing cohesive energy density. Equation (21) requires that μ should be large for the liquids of lowest E_{00}, pass through a minimum for the liquids having $E_{00} \sim E_{rr}$, and then increase again. Corresponding with these changes of μ, the liquids having greatest solvent or swelling power should be found at that point of the range where $E_{00} \sim E_{rr}$. In general, E_{rr} is not known, although it can be estimated approximately from the chemical nature of the polymer. A quantitative estimate may be made by using a cross-linked polymer, finding the liquid having the greatest swelling power, and then assuming its cohesive energy density to be equal to that of the polymer.* Given E_{rr}, a plot of the maximum swelling Q_m in this range of liquids against $(\sqrt{v_0})(\sqrt{E_{00}} - \sqrt{E_{rr}})$ should, according to equation (21), give a smooth curve, on which liquids of different chemical type should all fall. This in general is not quite true, but it holds surprisingly well for the swelling of natural rubber vulcanisates in a wide range of aliphatic liquids (Gee, *Trans. Inst. Rubber Ind.*, 1943, **18**, 266), as is shown in Fig. 4. The five curves are for very different compounds, and it is clear that there is no essential difference between their swelling behaviour. Aromatic liquids have in general a greater swelling power than aliphatic, for a given value of the abscissa (Gee, *loc. cit.*, 1942). With some of the more polar synthetic rubbers, different groups of aliphatic liquids do not fall on the same curve, although as

FIG. 5.



Swelling of a thiokol RD *vulcanisate in a range of aliphatic liquids.*
Curve 1 : *Esters.* *Curve* 2 : *Ketones.* *Curve* 3 : *Nitriles.*

illustrated in Fig. 5 the positions of the maxima usually agree. In order to fit the data quantitatively it is therefore necessary to generalise equation (21) empirically to the form

$$\mu = \mu_0 + \beta \frac{V_0}{RT}(\sqrt{E_{00}} - \sqrt{E_{rr}})^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (22)$$

where μ_0 and β may be somewhat dependent on the chemical natures of the liquid and the polymer. This limitation is not sufficient seriously to diminish the usefulness of this method of approach to the converse problems of selecting (*a*) polymers having solvent resistance and (*b*) solvents and plasticisers.

Conclusions.—In this brief survey, an attempt has been made to outline the statistical thermodynamic approach to the equilibrium properties of polymer solutions. It is clear that current theories, although crude, do give a surprisingly accurate quantitative account of the free energy of dilution. The separate calculations of the heat and entropy of dilution are less satisfactory, particularly in the region of dilute solutions, where a new statistical approach appears to be required. A more adequate statistical treatment of polymer–liquid systems, in which the heat of dilution is large or in which considerable volume changes occur, will almost certainly have to await advances in the understanding of the liquid state. Notwithstanding these limitations, the theory in its present form is capable of giving a semi-quantitative answer to a number of practical problems. One of these has been discussed above; a similar order of agreement between theory and experiment can be obtained in the other problems listed in the introduction.

* This process can be refined by using a graphical method of finding the maximum of the swelling–E_{00} curve (Gee, *loc. cit.*, 1943).

6. *The Study of Macromolecules by Infra-red Spectroscopy.*

By H. W. Thompson.

I can do no more today than mention some of the principles underlying the application of infra-red spectroscopy to the study of macromolecules, and give a few examples to illustrate them. In recent years a survey has been made of the spectra of many classes of substance in order to discover the kind of information which they may give (*J.*, 1944, 1833; Torkington and Thompson, *Proc. Roy. Soc.*, 1945, *A*, **184**, 3, 21; *Trans. Faraday Soc.*, 1945, **41**, 246). We have now reached a stage when more detailed work on particular aspects may be more profitable.

There is now no sharp boundary between the infra-red region and that of ultra-short radio, or micro-waves, and I ought to mention that very significant information about the properties of rubbers and plastics is now being obtained from work in the latter region. We are, however, mainly concerned today with the region of wave-length 1—25 μ, which is most easily explored experimentally. In this range the absorbed energy excites molecular vibrations, which may range in value from 50 to 3600 cm.$^{-1}$. However, the changes of molecular dipole moment associated with the different vibrations will vary considerably, and in consequence some vibrations are strongly excited in the infra-red, others more weakly, and some so feebly as to escape detection. Also, with complex molecules built up from recurring groups, there is often a grouping of some of the frequencies around particular values. These factors lead to a simplification of the spectrum as a whole, and while the spectra of many macromolecules remain complex and not fully interpretable in terms of a vibrational assignment, others are even simpler in general appearance than the spectra of those containing only half a dozen atoms.

Recent progress with complicated molecules has been due to two causes. First, recording spectrometers are now available with which a wide spectral range can be measured rapidly (Sutherland and Thompson, *ibid.*, p. 174; Wright, *Ind. Eng. Chem. Anal.*, 1941, **13**, 1; Barnes, Williams, and Liddel, *ibid.*, 1943, **15**, 83, 659; Barnes, McDonald, Williams, and Kinnaird, *J. Appl. Physics*, 1945, **16**, 77; Roess and Dacus, *Rev. Sci. Instr.*, 1945, **16**, 164; Whiffen and Thompson, *J.*, 1945, 268), and the technique of handling solid films and insoluble powders has been much improved. Secondly, much more is now known on the theoretical side about the correlation of vibration bands with particular types of vibration of the different nuclear skeletons. Ideally, greater progress would be made with these correlations if it were possible to treat the vibrations of complex molecules mathematically as mechanical models or lattices subject to harmonic oscillations. Although some attempts have been made in this direction, little has yet been achieved, as might be expected in view of the complicated inter- and intra-molecular interactions. We must therefore proceed at present by an essentially empirical method, in which the correlation of frequencies with structure is based upon comparisons of the spectra of related series of molecules (see, *e.g.*, *Proc. Roy. Soc.*, 1945, *A*, **184**, 3; *J.*, 1944, 303, 597; 1945, 640).

The use of the infra-red spectra is essentially analytical, and is governed by two main considerations. Since the molecular vibration frequencies are determined in magnitude by the nuclear masses and the interatomic forces, any molecule will have a characteristic set of frequencies, differing in principle at least from the set for any other molecule except an optical enantiomorph. In practice, of course, with two molecules of great complexity and close similarity, the difference in the vibrational spectra may be slight, and require more elaborate methods—higher resolving power—for detection. The second consideration is that, although a molecule vibrates as a whole, a favourable conjunction of circumstances may lead to the result that in some of the vibrations certain linkages or groupings effectively control the oscillation, so that the frequencies characteristic of a group may appear almost unchanged in all molecules containing it. For example, linkages involving hydrogen such as C–H, O–H, N–H, S–H or Si–H each have an almost constant frequency; the same is true of double bonds such as C:C, C:O, or C:N, while groups such as the acetyl or *tert.*-butyl radical or the ether linkage C–O–C also give rise to almost constant sets of frequencies. The greater precision of recent measurements has made it possible, moreover, to infer from the small variations in the frequency of certain groups the exact nature of the other groups attached to them.

The applications of these principles can be classified roughly as follows: (i) the measurement of the rate and mechanism of polymerisation reactions, (ii) the elucidation of the structure of molecules of a polymer or other macromolecule, (iii) the derivation of facts likely to bear upon the order or arrangement of the macromolecules in a given state of aggregation, (iv) the study of changes brought about by special treatment of a macromolecule affecting its physical or

chemical behaviour, (v) the general analysis of mixtures of macromolecules, or other analytical problems which are less easily tackled by other methods. This analysis can be either empirical, or based upon a theoretical background of one sort or another.

The rate of polymerisation of an unsaturated molecule such as styrene, *iso*butylene, methyl acrylate, or the condensation of butadiene with a vinyl derivative can be followed either by measuring the rate of disappearance of the vibration band due to the unsaturated C:C bond, or of the appearance of some band due to the polymer (Barnes, Williams, and Liddel, *loc. cit.*, p. 659). The unsaturated link gives rise to a band in the region of 1650 cm.$^{-1}$, but if a band of the product is to be used it must of course be chosen, after measuring the spectra of starting materials and product, so as to be as distinct as possible. In the past, the procedure has been to remove samples of the reacting mixture at stages of the reaction, and then measure their spectrum over the required spectral range, using standard experimental conditions. Two other methods of analysis now promise to revolutionise the whole method. In one, an infra-red analyser is used, comprising a system of differential filters by means of which some fairly narrow selected spectral range of radiation is passed through the material and the transmitted energy is recorded continuously (Luft, *Z. techn. Physik*, 1943, **5**, 97).* This obviates the use of a spectrometer, and provides a robust, subtle instrument of wide applicability, particularly in gas analysis. It seems possible that fairly soon the use of such apparatus will make the automatic control of flow lines possible. The other development is the use of extremely rapid infra-red detectors with a spectrometer in which the prism is rotated rapidly, and a trace of the spectrum obtained on the screen of a cathode-ray tube. By this means the spectrum is scanned very rapidly, and part of it can be watched continuously. Such an instrument was first developed by Baker and Robb (*Rev. Sci. Instr.*, 1943, **14**, 362), and an improved model has now been described by Daly and Sutherland (*Nature*, 1946, **157**, 547). We are building another instrument of this kind in my laboratory (*ibid.*, 1946, **158**, 196).

The spectrum of the reaction mixture or product may also indicate the mechanism of the reaction. In the condensation of butadiene, for example, either 1 : 4- or 1 : 2-addition can occur, leading respectively to a skeleton of the type $R_1{\cdot}CH{:}CH{\cdot}R_2$, and to pendent vinyl groups ($-CH{:}CH_2$). Criteria are now available for differentiating the various kinds of olefinic linkage (*Proc. Roy. Soc.*, 1945, *A*, **184**, 3), so that the relative proportions of the two types can be estimated. This method can be applied in the same way to condensation of butadiene with styrene or acrylonitrile, or the polymerisation of other dienes such as isoprene. It has served very well to indicate the different proportions of 1 : 2- and 1 : 4-addition in the polymerisation of butadiene by different methods, for example, with sodium, potassium, or by emulsion polymerisation; and in many cases seems a quicker and more reliable guide than chemical methods such as ozonolysis. There are still some outstanding difficulties in making it more accurate, such as the problem of obtaining films of known and uniform thickness, and the more fundamental question of whether the extinction coefficients of the key bands for the different types of nuclear skeleton remain sufficiently constant in different molecules. A similar instance in which the spectrum reveals the course of polymerisation is the detection of polystyrene in some samples of a copolymer of butadiene with styrene.

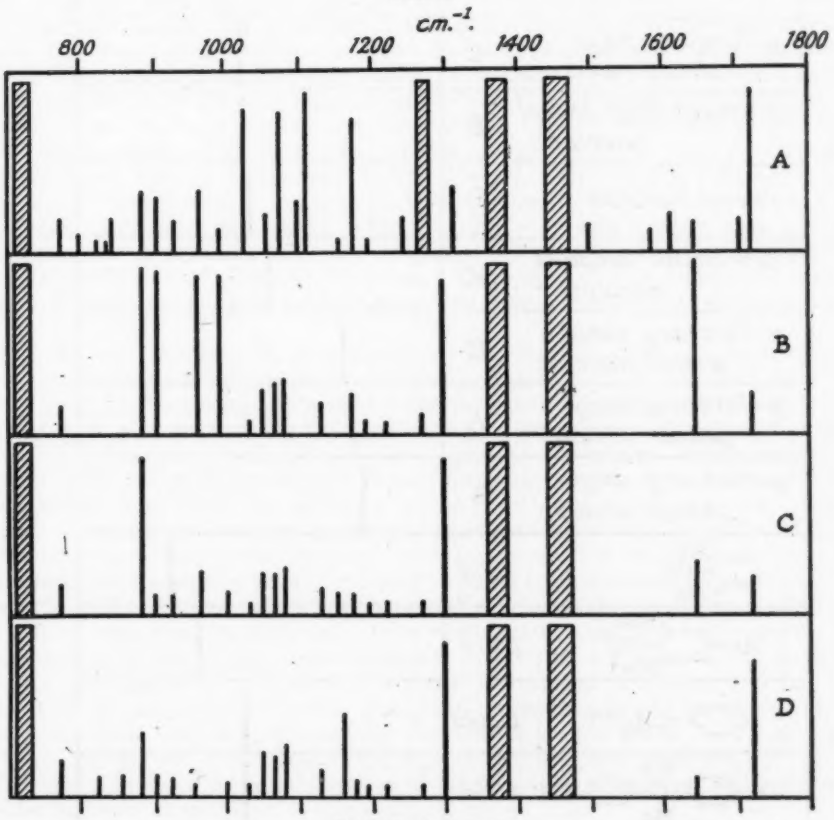
The presence in a macromolecule of unexpected groups can also be revealed by the spectrum. For example, methyl groups in polythene are shown by characteristic bands near 3·4 μ and 7·2 μ, and their number can be estimated from the intensities of the key bands. Similarly, C:O and C:C linkages can be found when present in small amount. Fig. 1 shows diagrammatically the spectra of four hydrocarbon waxes made in different ways, and almost indistinguisable chemically though differing in physical properties. All the samples show the main features of a long-chain paraffinic hydrocarbon with some side chains. In addition, however, *B* shows bands in the region 850—1000 cm.$^{-1}$ due to the deformational vibrations of different types of olefinic skeleton, *D* has well-marked bands at about 1165 and 1720 cm.$^{-1}$, indicating carbonyl (probably $CH_3{\cdot}CO$) groups, and *A* shows many bands suggesting both ketonic and aromatic groupings. The variation of intensity of the bands at about 1640 and 1720 cm.$^{-1}$, which indicate C:C and C:O groups respectively, is important. It becomes clear that small differences in the methods of preparation can thus be revealed, which may have an important bearing not only upon the value of the products but also on an understanding of the reactions involved. For example, it seems possible to correlate the dielectric loss factor of such materials with the content of the particular polar groups. It may also be noted that a quantitative determination of groups such as C:O and C:C can be made

* British and American instruments of this kind will be described shortly.

from the measured intensities, down to very small concentrations. Oxygen of a carbonyl group embedded in a hydrocarbon such as polythene can be determined down to 0·01% or less, but naturally such high sensitivity will only apply in the most favourable cases where the intrinsic extinction coefficient of the important band far exceeds those of the other vibration bands of the molecule, or when the particular band being examined lies in a region where overlap by other bands is very small and thicker layers of material can be used without obscuring the issue.

A natural question is whether the spectrum affords any direct clue to the molecular weight of a polymer. As regards the arrangement—positional frequencies—of the bands, it does not. Thus, while some small changes occur in the position of bands of lower normal paraffinic hydrocarbons as the chain length increases, with more than about ten carbon atoms the spectrum

FIG. 1.



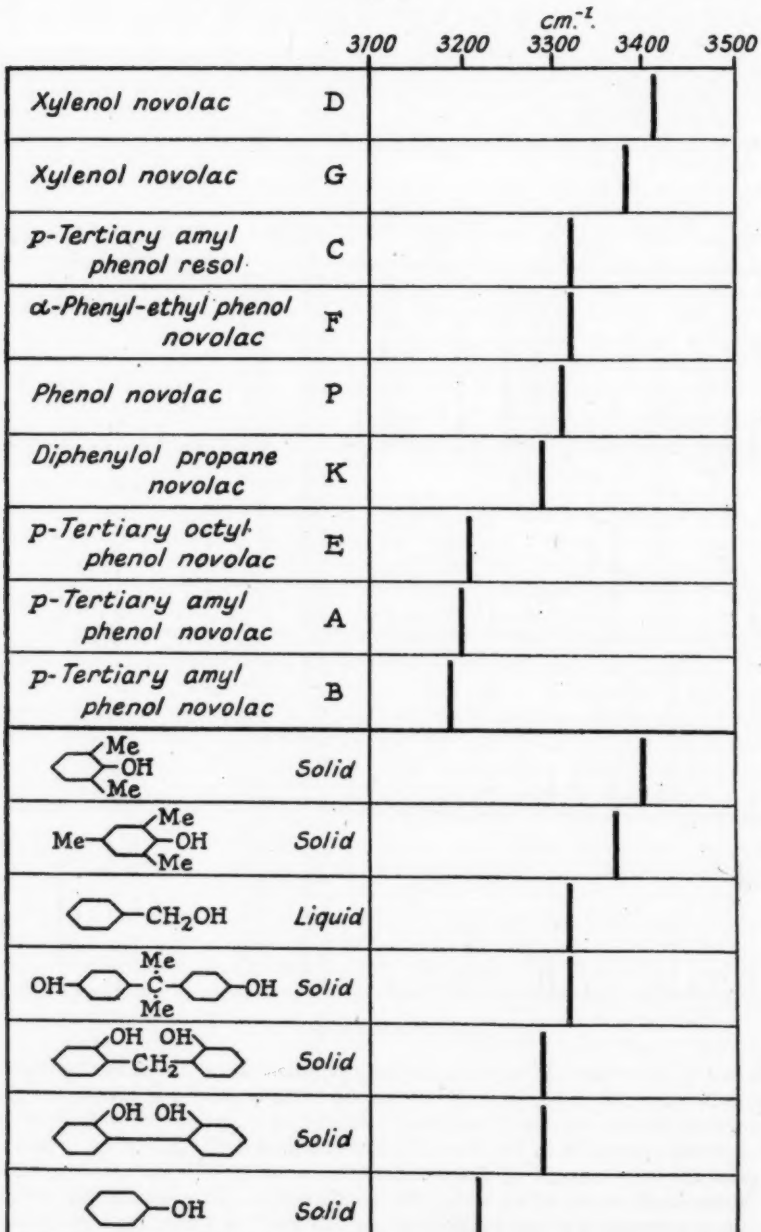
Hydrocarbon waxes.

is hardly affected. The same has been found with poly*iso*butenes of molecular weight between 1000 and 100,000, and with other polymers built up from a recurring skeleton. On the other hand, a careful examination of the intensities of bands, as opposed to the frequencies, and the determination of end groups, may lead to estimates of the chain length in some cases. We thus encounter again the new aspect of infra-red work, namely, the accurate measurements of intensities. Some exploratory work which Mr. Mann and I have been doing suggests that in normal paraffins the intensity of the band at about 725 cm.$^{-1}$ is determined by the length of the hydrocarbon chain. Such relationships may be very useful.

Another similar problem is the determination of the disposition of particular side-chain groups in a long molecular chain. It has been found, for example, that the spectra of polyvinyl chloride and polyvinylidene chloride differ from those of halothene (chlorinated polythene) having the same percentage of chlorine, and this must be interpreted as being due to a different arrangement of the chlorine atoms along the carbon skeleton in the different cases (*Trans.*

Faraday Soc., 1945, **41**, 255). The spectra of simple chloro-paraffins suggest that it may be possible to obtain correlations for the detection of $-CHCl-$ or $-CCl_2-$ groupings, and the frequencies of C–H bonds are also affected by the proximity of halogen atoms. Also, the

FIG. 2.



presence in a skeleton of a chain of four or more carbon atoms may be revealed by the band at about 725 cm.$^{-1}$. By such diagnostic methods, as well as by measurements of the intensities of bands, it is worth tackling the problem just indicated. The same applies to the determination of the number and position of hydroxyl groups in an interpolymer of ethylene with vinyl alcohol.

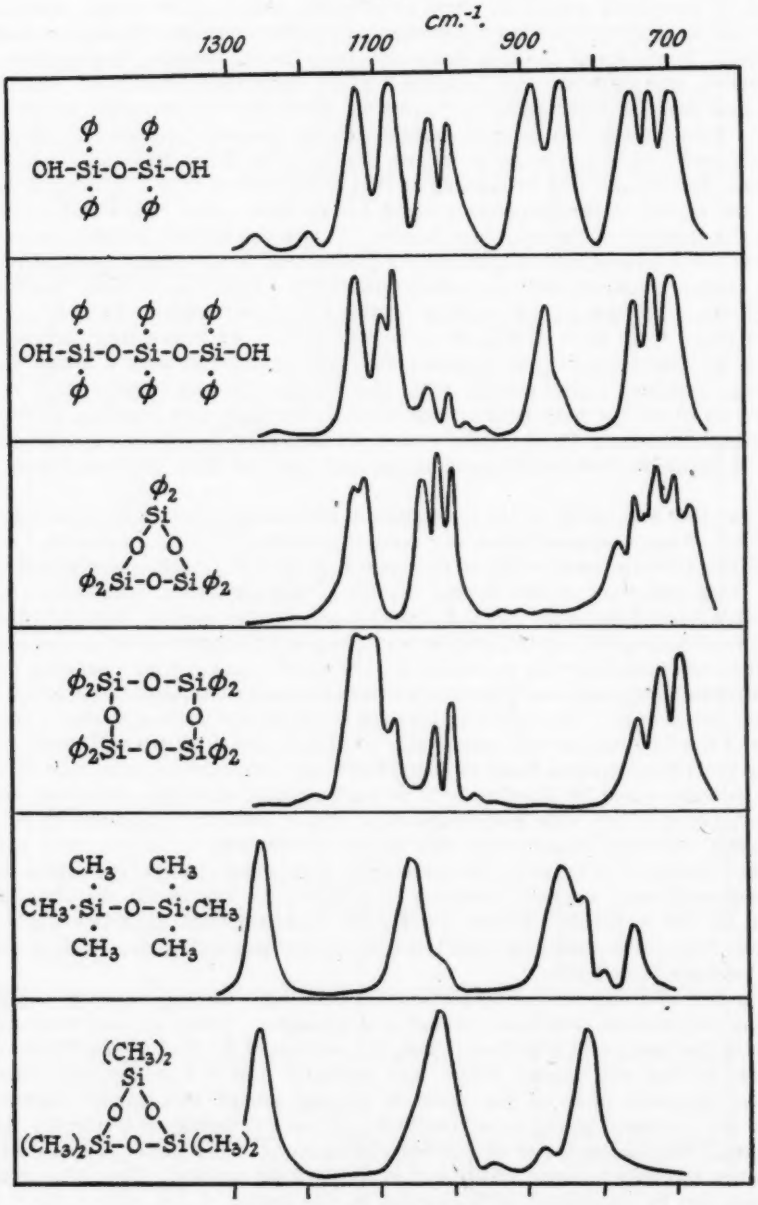
I will refer briefly to some other points which arise with other kinds of macromolecules. A number of condensates of phenols with aldehydes have been examined. There are noticeable differences between the spectra of novolacs made from formaldehyde and differently substituted phenols, which are in part due to the different substituents on the aromatic nuclei but may also arise from differences in the method of condensation. The spectra of a resin on the one hand, or resol on the other, made from a given phenol and formaldehyde, show differences which can to some extent be correlated with differences in structure, and another rough correlation rule has been found for finding the positions through which the aromatic nuclei are linked together (*ibid.*, p. 258). Some small changes have also been found between the spectra of one- and two-stage resins, and between the " fusible " and " infusible " varieties. Although some of the differences can be interpreted in terms of structure, many must at present be used empirically. One unexpected feature promises to be specially important. It is well known that the " normal " hydroxyl group gives rise to a band at about 3600 cm.$^{-1}$ which is displaced towards lower frequencies and broadened if this group enters into a hydrogen bond. In the latter case the centre of the association band lies at 3100—3400 cm.$^{-1}$ and its exact position depends on the strength of the hydrogen bonds. It appears that in novolac resins made from a given aldehyde but from different phenols the position of the hydroxyl association band varies over a wide range. Some examples are shown in Fig. 2. In the substituted phenols themselves there is a similar variation in the position of this association band. Details are given in a forthcoming paper with R. E. Richards in this *Journal*. An interesting feature is that there seems to be no direct connexion between the positions found with a given phenol and its corresponding novolac. The results with the simple phenols suggest that screening and steric influences of groups may minimise or weaken the hydrogen bonding, and presumably a similar interpretation may apply to the resins. There may well be some correlation between the degree of hydrogen bonding in such resins and some of their physical characteristics and behaviour.

A start has also been made in the construction of correlation rules for compounds of silicon, with the object of examining silicones and related compounds (R. E. Richards, to be published shortly). Straight-chain compounds of the type $R_3Si{-}[OSiR_2]_n{-}SiR_3$, in which R is an alkyl or aryl group, ring polymers of the type $[{-}R_2SiO{-}]_n$, alkoxysilanes, silicols and other related molecules have been examined. Fig. 3 shows some of the spectra over a small range. It seems possible to distinguish, empirically at least, between the open-chain compounds on the one hand and the corresponding ring polymers on the other; and if high resolving power is used, and the relative band intensities are carefully measured, to differentiate polymers of a given type with different values of n. The hydrogen-bonding relationships in the silicols are also interesting. Correlations of the frequencies with specifically localised vibrations are still somewhat tentative, although the Si–H bond gives a band at about 2240 cm.$^{-1}$, and the vibrations of alkyl or alkoxy-groups can in some cases be assigned. It is worth noting that the deformational frequency of the methyl group found with hydrocarbons at about 1375 cm.$^{-1}$ appears to be displaced to another roughly constant value when this group is attached to silicon, and the differences between about 10 and 12 μ between the open-chain compounds having the group $-Si(CH_3)_3$ and the ring compounds may suggest vibration frequencies for the group $-Si(CH_3)_3$ analogous to those found for the *tert.*-butyl group $-C(CH_3)_3$ in hydrocarbons at about 8 μ. Preliminary results suggest that much useful information about the silicon derivatives will be obtained from the spectra between 12 and 30 μ.

Another group of compounds worth attention comprises those containing the peptide link, such as nylon, polyamides, polyester-amides, and proteins. There are two main aspects in the examination of the spectra of this class: first, the regions of 3 μ and 5—7 μ where vibrations of the $-CO{-}NH-$ groups will usually occur, and secondly, the rest of the spectral range where bands due to the main body of the chain or to side groups will occur. Differences in the character of the carbonyl group as a result of hydrogen bonding or electronic influences are revealed in small displacements of the carbonyl frequency. The latter is found at about 1720 cm.$^{-1}$ in ketones, but falls to about 1640 cm.$^{-1}$ in simple solid amides. The shifts in this carbonyl frequency can also be correlated with changes in the region of 3 μ, where the " normal " or " bonded " N–H vibration frequency will occur (*J.*, 1944, 301). We have also found differences between the spectra of fibroin before and after denaturation, although a complete interpretation of them cannot yet be made. This is a field in which progress must at present be empirical, and before any real contribution is made towards the chemistry of proteins, more must be understood about the spectra of amides and amino-acids and the nature of the peptide linkage in such simpler systems (Richards and Thompson, *J.*, in the press).

We have carried out similar measurements with cellulose, esters of cellulose, and their degradation products (I. F. Trotter, to be published shortly). Again, as a possible background of reference, the spectra have been measured of a large number of simple sugars and their derivatives. Over the range 5—15 μ these substances have very complex spectra, an analysis of

FIG. 3.



Derivatives of silicon.

which is at present impossible, although they provide numerous examples of two very closely related molecules having marked spectral differences. Some correlations are possible, and it may be possible to differentiate between primary and secondary alcoholic groups, a useful point in connexion with the work on cellulose esters. Some promising results have been

obtained in the detection of particular groups in the degradation products of the celluloses, but there is no doubt that the interpretation of the spectra of this type of compound can only be limited. As in the case of some of the other classes already mentioned, however, there appear to be some peculiar variations in the bands due to hydroxyl groups in the different molecules, and in this spectral range around 3 μ work with higher resolving power should be profitable. In this region it seems likely that the rôle of hydrogen bonding in the swelling of cellulose esters by special reagents can be examined.

Among the processes involving special treatment of macromolecules I should mention vulcanisation and oxidation of rubber, plasticisation, and the effect of ultra-violet radiation or of heat. All these topics have been explored in special cases. When crepe rubber is vulcanised by sulphur chloride new bands appear in the spectrum, and others disappear (Torkington and Thompson, *Trans. Faraday Soc.*, 1945, **41**, 276). The problem is to correlate these bands with the formation or destruction of linkages such as C–S, S–S or C=C. For this purpose reference spectra of thiols, sulphides and disulphides have been measured, and key bands have been deduced for the C–S bonds (Trotter and Thompson, *J.*, 1946, 481). The vulcanisation of rubber by sulphur and other reagents has also been followed in the infra-red spectrum (Sheppard and Sutherland, *Trans. Faraday Soc.*, 1945, **41**, 262), and it is interesting to compare the results with those obtained for the alternative process. In the oxidation of rubber, OH, C=O, and possibly other groups are formed. The spectrum shows new bands near 3 μ, 6 μ, and 9 μ and in other regions. There is still some doubt about the interpretation of the fresh absorption near 9 μ, since several groupings, including the ether linkage, lead to bands at about this wave-length. However, in some cases such as that of polythene mentioned above, the carbonyl and hydroxyl groups can be determined even when present in only small amount. Further work is required by this method on the oxidation of rubber itself. Some experimental difficulties still remain in this connexion, such as the preparation of suitable films in which the interference from fillers such as carbon black is avoided or minimised.

An alteration in the mode of packing of fibrous molecules in the solid or the liquid state might in principle be expected to affect the vibrational spectrum, since there should be a change in the force field or potential-energy function, as well as in the symmetry of the assemblage. We should expect that effect to be relatively more marked with molecules containing polar groups. In the case of rubber it might lead to alteration in the spectrum upon stretching, and there is some evidence in support of this (Williams and Dale, *J. Appl. Physics*, 1944, **15**, 585). On the other hand, no differences have yet been found between the spectra of the sol and the gel form of rubber. With molecules capable of molecular orientation in the solid state, for example, nylon, polythene, and polyvinylidene chloride, there should be a change in the relative intensities of bands if the sample is examined in plane-polarised radiation with the direction of orientation of the chains successively parallel and perpendicular to the plane of polarisation (*Proc. Roy. Soc.*, 1945, **184**, *A*, 3). This effect has been examined with oriented polythene and nylon, and small changes in the relative intensities of bands have been found. Further measurements on the phenomenon are desirable.

From the examples which I have cited it is clear that valuable information on a number of points can be obtained. It is equally evident that the infra-red method cannot provide other data such as are obtained from *X*-ray measurements, and the two methods should be regarded as complementary to each other and to other physicochemical lines of work. If the infra-red diagnosis is to be really successful it is necessary that much other knowledge be first obtained about the structure, so that the spectroscopic evidence can be used to decide between two or three possible alternative formulations.

I should refer finally to the general problem of analysis by infra-red methods (Sutherland and Thompson, *loc. cit.*, p. 197; Wright, *loc. cit.*; Brattain and Beeck, *J. Appl. Physics*, 1942, **13**, 699; Barnes *et al.*, *ibid.*, 1945, **16**, 77; *Ind. Eng. Chem. Anal.*, 1943, **15**, 659; Nielsen and Smith, *ibid.*, p. 609; Thompson, *J.*, 1944, 183; *Analyst*, 1945, **70**, 443). It is now possible, for example, to use key groups for the cyano-group (about 2230 cm.$^{-1}$) or phenyl radical (about 750 cm.$^{-1}$) to estimate the amount of acrylonitrile or styrene taken up in copolymerisation with butadiene, although for accurate quantitative work there still remains the difficulty of obtaining films of known and uniform thickness. It is possible also to estimate acetyl, propionyl, or butyryl groups in a cellulose ester or mixed ester. In cellulose acetate there are bands in the region of 3 μ due to stretching vibrations of the methyl groups and of the un-acetylated hydroxyl groups, and by empirical calibration of the change in relative intensities of these bands as the acetylation proceeds, a fairly precise estimate can be made of the percentage of acetyl groups when the latter is in the range 50—60%. By using key bands for the separate isomers, mixtures

of natural and synthetic rubbers can be analysed (Barnes, Williams, Davis, and Giesecke, *Ind. Eng. Chem. Anal.*, 1944, **16**, 9).

Future work in this field may proceed along four main lines. First, more correlation rules are required for structural diagnosis, and a more thorough study should be made of hydrogen bonding where it is relevant. Secondly, the whole question of the intensities of bands must now be examined, in order to supplement structural diagnosis based upon the independent method of correlation by frequencies. Thirdly, measurements with grating spectrometers giving higher resolving power should lead to a more exact knowledge in some cases. Finally, use should be made of the newer types of infra-red recorder, either the analysers based upon special filters for following reaction rates, or the oscilloscope method of observing an infra-red spectrum continuously, so that changes can be observed as they actually take place.

Discussion.

DR. G. B. B. M. SUTHERLAND: It might be useful for people to have a few more details of the performance of the "instantaneous" infra-red spectrometer (referred to by Dr. Thompson in his paper) which has been developed at Cambridge by Mr. E. F. Daly and myself, as it may have direct applications to polymerisation problems. Our purpose was to get a continuous picture of an infra-red spectrum, so that when the spectrum altered because of chemical reactions or other causes, the changes in the spectrum would be literally visible. For instance, this would enable one to follow chemical reactions going too fast to be studied by the usual sampling method. By using a very fast bolometer as the radiation detector, we are able to scan in 14 seconds a range of about 2 mμ in any region of the spectrum between the visible region and 15 mμ. The spectrum is displayed on a cathode-ray screen of such long persistence that, when the spectrum begins to be retraced (after 14 seconds), the afterglow from the preceding trace is still strong enough to be easily visible. Although the applicability of this instrument is at present limited to reactions completed in a few minutes, it should be possible to increase the speed of scanning considerably in the future, particularly if one is prepared to restrict the region scanned. The slide now shown illustrates the picture obtained of the spectrum of 2 : 2 : 4-trimethylpentane between 7 and 9 mμ. The five absorption bands at 7·3, 7·8, 8·0, 8·3 and 8·6 mμ are seen to be well resolved.

There are, of course, many points which one would like to discuss at length in Dr. Thompson's paper, but in view of the late hour I shall confine myself to two questions. First, in the spectra of certain silicone polymers, differences were remarked which appeared to be reliable in classifying these into straight chain or cyclic compounds. Has Dr. Thompson any interpretation of this spectroscopic difference and how it might be related to the structural difference? Secondly, what interpretation would Dr. Thompson give to the difference between the spectra of the raw and denatured silk fibroin?

Is not part of the answer to the question whether more accurate determination of band positions would enable us to detect still finer changes in structure that we are not seriously limited by resolving power of the spectrometers now used. It is the natural widths of the bands in the liquid state which generally prevent more accurate determination of differences.

DR. J. L. STOVES: I am very interested in Dr. Thompson's reference to the importance of hydrogen bonds in macromolecular systems. In this connexion I should be pleased to learn if there is any hope of applying infra-red spectroscopy to a study of the rôle of hydrogen bonding in certain gross-structural changes occurring in fibrous proteins, I refer to the hydrothermal shrinkage of collagen and to the supercontraction of keratin fibres. Recently, Gustavson (*J. Amer. Leather Chem. Assoc.*, 1946, **41**, 47) has brought forward evidence which suggests that the shrinkage of collagen in water at temperatures above *ca.* 60° is due to fission of hydrogen bonds between intermolecularly co-ordinated peptides, rather than to rupture of side-chain linkages. In the case of keratin, supercontraction is usually associated with fission of cystine disulphide and salt linkages; rupture of hydrogen bonds, however, may be of considerable importance. Can infra-red spectroscopy help in elucidating the mechanisms of these phenomena?

MR. W. COOPER: Zinke and his co-workers (*Ber.*, 1942, **75**, 151) have shown that phenolic ethers of the type ·Ar·O·CH_2· are formed during the resinification of condensates from phenols and formaldehyde, and these break down at high temperatures to give numerous other products. Much other evidence including that from infra-red spectroscopy (Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 258) has been adduced to show the presence of methylene linkages between the aromatic nuclei. Suggestions have been made (Redfarn, *Brit. Plastics*, 1942, 481)

that in the cross-linking of phenolic resins, where the normal reactive positions in the nucleus are occupied, reaction occurs involving the phenolic hydroxyl to give ether linkages.

It would be interesting to know whether these ether groupings have been detected at any stage and, if so, to what extent they are present.

MR. FRANK BROWN : Could Dr. Thompson give any information on the use of infra-red spectroscopy in distinguishing between true copolymerisation (*e.g.*, between two monomers, A and B) as opposed to simultaneous individual polymerisation ?

DR. THOMPSON : Apart from the instance quoted in the lecture, *e.g.*, the copolymerisation of vinyl and vinylidene chloride where small amounts of separate polyvinylidene chloride were detected, I am not aware of any other instances. It will probably be possible, however, to apply infra-red spectroscopy for the above purpose in certain cases.

As regards the assignment of bands with the silicon polymers, it is too early yet to be very definite. Although we have now measured a fairly comprehensive set of compounds the obvious correlations are few, except for those already mentioned. We hope to report in detail on these results soon.

Similarly, more work has yet to be done before the spectral changes in denaturation can be fully explained. There are marked alterations near 3 μ and between 6 and 10 μ which can be tentatively correlated with changes in hydrogen bonding and also of side-chain groups.

There are also not yet sufficient data to answer some of the other interesting questions raised. In some cases too it is not possible to predict whether the infra-red method is going to give a clear answer without actually measuring the spectra involved, since we cannot yet predict exactly enough the positions and intensities of bands with some of the more complex molecules.

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7. *The Study of High-polymer Structure by X-Ray-diffraction Methods.*

By C. W. BUNN.

THE information obtainable by a study of high polymers by *X*-ray diffraction methods is geometrical in character. In favourable circumstances it is possible to determine with fair precision the configuration of the molecules (or rather, of sections of molecules) and the way in which they are arranged. Usually the detailed interpretation of *X*-ray diffraction patterns in terms of molecular configuration and arrangement is only attempted for polymers of known chemical structure : interpretation might possibly be achieved for polymers of doubtful chemical constitution, in which case the chemical constitution would be settled by the *X*-ray method; but the difficulties are severe, and this has not been done so far. The contributions of *X*-ray methods, being mainly stereochemical, are thus complementary to those of infra-red methods, which are concerned largely with questions of chemical constitution.

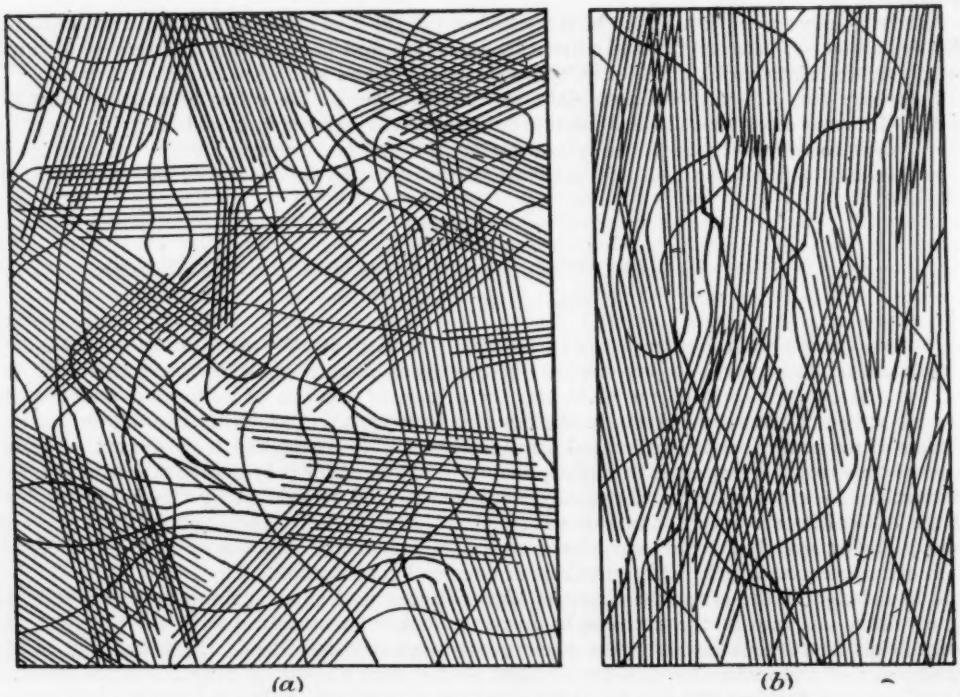
A knowledge of the stereochemistry of high-polymer molecules is important, not only for its own sake, but also in the attempt to correlate molecular structure with the physical properties which give to high polymers their great practical usefulness. A knowledge of the arrangement of the molecules may throw light on the part played by intermolecular forces in determining the physical and mechanical properties of particular polymers. It is also possible to obtain from *X*-ray diffraction photographs other types of information which relate to the texture of specimens prepared in particular ways : information about the size and orientation of those ordered regions we call crystalline—information which is of great practical value in understanding the variations of the properties of high polymer specimens treated in specific ways—but I shall not deal here with questions of texture; I shall confine what I have to say to questions of stereochemistry and molecular arrangement.

Detailed interpretation of *X*-ray diffraction patterns in terms of molecular configuration and arrangement is not always possible, even when there is no doubt about the chemical structure of the molecules. If an *X*-ray beam is sent through a small specimen of a glass-like polymer, such as polystyrene or polymethyl methacrylate, a pattern of very diffuse rings is obtained : this is evidence of lack of any ordered molecular structure, and it is obviously not possible, from two or three diffuse rings, to deduce anything very certain or precise. On the other hand, other polymers, such as polythene, the polyesters and polyamides, give patterns showing a number of fairly sharp diffracted beams; for these polymers there is a possibility of detailed interpretation, though this has only been achieved so far for polymers of comparatively simple chemical structure. The fairly sharp diffraction patterns given by these polymers are evidence that the molecules are precisely arranged, and such polymers we call crystalline. They are

not completely crystalline: there is usually, in addition to the pattern of fairly sharp reflections, a diffuse ring showing the presence of a certain proportion of disarranged molecules.

How is it that molecules of high polymers are able to arrange themselves in a precise manner to form a largely crystalline mass? This is best approached by forming a mental picture of a melted polymer: very long-chain molecules of irregular configuration are tangled together, and are continually wriggling and changing their configurations by rotation round single bonds. When the specimen is cooled, those sections of chains which happen to be approximately straight can pack parallel to each other to form small crystalline regions which then grow by accretion of parts of other molecules. As a result of this process, any one molecule, in the course of its length, may pass through a number of different crystalline regions; where it wanders from one crystalline region to another, there is no regular arrangement, and such pieces of molecules constitute the amorphous regions (see Fig. 1, *a*).

FIG. 1.

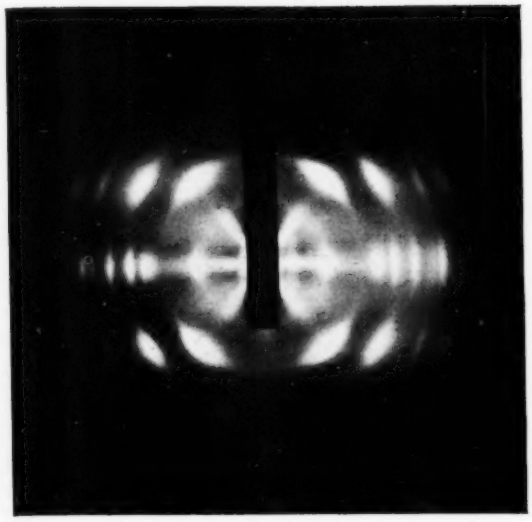


(*a*) (*b*)

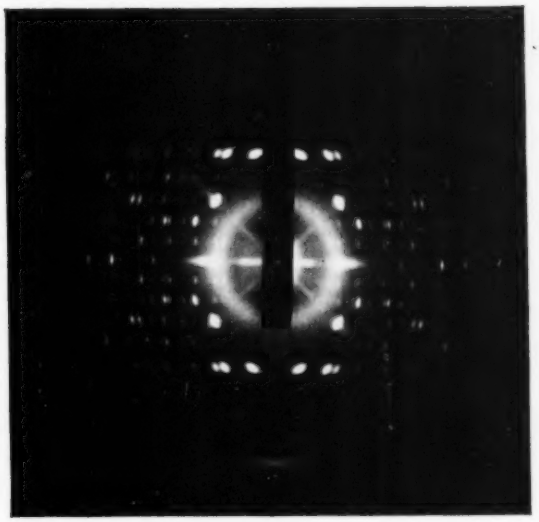
(a) *Two-dimensional representation of structure of crystalline polymer.*
(b) *Structure of drawn fibre (direction of drawing vertical).*

Such a specimen of a crystalline polymer, produced by cooling, gives an *X*-ray diffraction pattern consisting of a number of complete rings; each ring may be regarded as the reflection of *X*-rays by a particular type of crystal plane (the ring being complete because crystals of all orientations with respect to the beam are present in the specimen); but unless we can gain some knowledge about the relative orientations of the different crystal planes, interpretation of the pattern is much too difficult and uncertain. To gain such knowledge of the mutual orientation of reflecting planes, we must get the crystals into something like order. This is usually done by drawing threads: the molecules are drawn into roughly parallel alignment (Fig. 1, *b*), and thus the crystalline regions which are formed by the regular side-by-side packing of sections of molecules all have one axis roughly parallel to the direction of drawing (the "fibre axis"). Rubber-like polymers, which are not crystalline at room temperature (being above their melting points), may sometimes be crystallised by stretching; but to preserve the crystallinity it is necessary to clamp the specimen in the stretched condition.

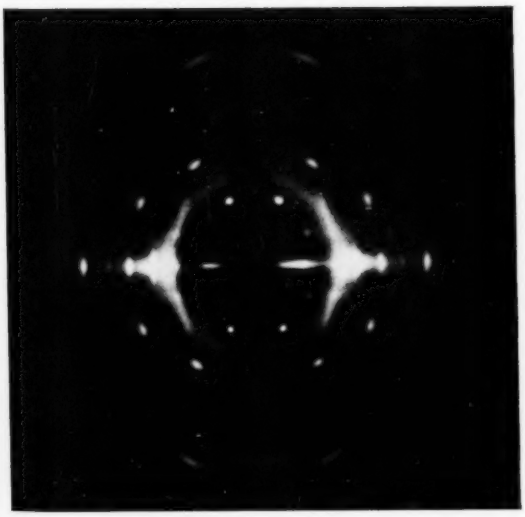
When an *X*-ray beam is sent through such a specimen at right angles to the fibre axis, the diffraction pattern produced (see Plate) shows spots or short arcs arranged in parallel lines



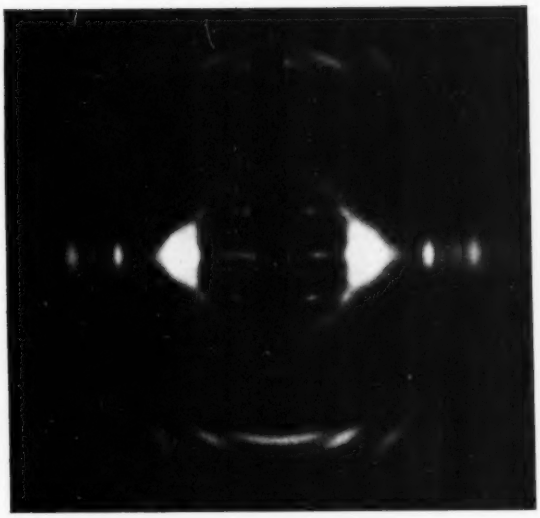
a.



b.



c.



d.

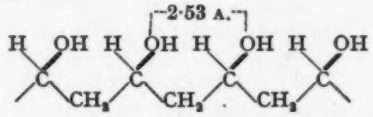
X-Ray diffraction photographs of fibres.

a. *Polyvinylidene chloride.*
b. *Polyisobutene.*
c. *Polyethylene adipate.*
d. *Polyhexamethyleneadipamide* (*nylon* 66).

[*To face p.* 298.

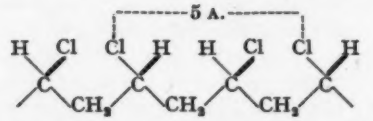
(" layer lines "). This is the type of photograph from which most of our information on the crystal structure of high polymers has been deduced. An additional type of orientation may sometimes be imposed by pressing or rolling fibres; particular crystal planes tend to set themselves in the plane of the sheet-like specimen thus produced; and such specimens, in their behaviour to *X*-rays, simulate single crystals or twinned crystals, and may be studied by the methods developed for single crystals.

For the simplest types of polymers it is sometimes possible to obtain valuable information in a very simple way. The repeat distance along the fibre axis is readily and directly determined from the spacing of the layer lines on the diffraction photograph; and since the crystal axis in this direction is also the molecular axis, the repeat distance is a distance *within* the molecule. Consequently, it is possible in the simpler cases to deduce with considerable confidence the complete stereochemistry of the molecule from the fibre repeat distance. Thus, in polythene the repeat distance is 2·53 A. (Bunn, *Trans. Faraday Soc.*, 1939, **35**, 482); this is just the repeat distance of a fully-extended carbon chain having a plane zigzag configuration (the interatomic distances and bond angles having the normal values C–C 1·54 A., C< about 110°), and therefore it appears that the chains in polythene have this configuration. The repeat distance in polyvinyl alcohol (Halle and Hofmann, *Naturwiss.*, 1935, **23**, 770; Mooney, *J. Amer. Chem. Soc.*, 1941, **63**, 2828) is the same as that of polythene, and therefore the configuration of the chains is similar; and further, it appears that in this substance the OH groups are all in corresponding stereo-positions, *i.e.*, all above or all below the plane of the zigzag, which is the plane of the paper in the following representation :

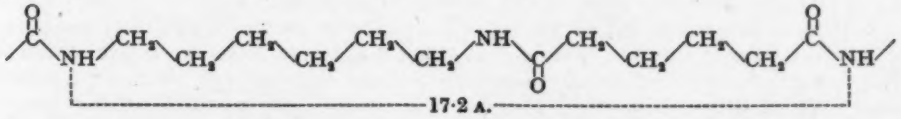


[For if they were, for instance, alternately on each side of the plane of the zig-zag (alternately above and below the paper), the repeat distance would be 2 × 2·53 A.] Thus, in this particular case, the complete stereochemistry of the molecule appears to be settled by one simple measurement on an *X*-ray diffraction pattern.

Polyvinyl chloride does not crystallise well: fibre diagrams can be obtained, but they are very diffuse, showing that the crystalline regions are very small or very imperfectly formed; however, the repeat distance can be determined approximately. It is 5·0—5·1 A. (Fuller, *Chem. Reviews*, 1940, **26**, 143), *i.e.*, double that of polyvinyl alcohol; it is therefore likely that the chain is a plane zigzag and that the chlorine atoms are alternately on each side of the plane of the carbon chain :



Whenever the fibre repeat distance for a particular polymer is the maximum to be expected in view of our knowledge of the chemical structure and the known bond lengths and angles, we can be reasonably certain of the configuration of the molecules. This is true for polymers with long repeat distances, no less than for the short-period polymers discussed so far. For instance, the repeat distances of the polyamides (Fuller, Baker, and Pape, *J. Amer. Chem. Soc.*, 1940, **62**, 3275) indicate that the chains are planar or very nearly so. Nylon 66, for instance (polyhexamethyleneadipamide), has a repeat distance of 17·2 A., and this is about right for a planar molecule of 7 zigzags comprising one chemical unit :

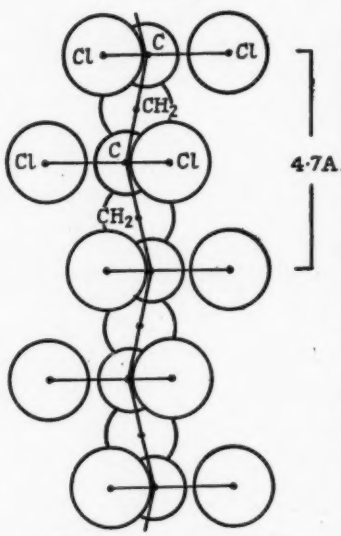


It is, of course, just possible that there might be a meandering or helical configuration of two or more chemical units in each geometrical repeat (much reduced in length by being curled up); but it would be a surprising accident if the repeat distance of such a chain happened to correspond with that of a fully-extended one-unit repeat. (In actual fact, a detailed inter-

pretation of the *X*-ray pattern has shown that the chain is indeed a simple zigzag with a one-unit repeat; see below.)

If, however, the measured fibre repeat distance of a polymer is appreciably less than that expected for a fully-extended chain, it is usually not possible to deduce the configuration, except in very simple cases. For, when there are many atoms in the repeating unit, there are many different ways of shortening the chain by rotation round single bonds; the question arises, " Round which bonds must rotation occur to give the required shortening? Or is there perhaps a small rotation round each bond? " And the greater the number of atoms in the repeat, the greater the number of possible ways of accounting for the observed shortening. The point is an important one and needs emphasis. Much of the discussion of the configuration of molecules of high polymers is based on fibre repeat distances and very little else. We have seen that this is sound if the repeat distance is the maximum, but is unsafe if it is appreciably less than the maximum; and it is increasingly hazardous with increase in the number of atoms in the repeat. For repeat distances of 10—20 A. (at least 8—16 atoms), where the shortening is an appreciable fraction of the length of the fully-extended chain, suggestions of configurations based on repeat distances alone must be regarded as preliminary speculations.

FIG. 2.



Configuration suggested for polyvinylidene chloride (Fuller).

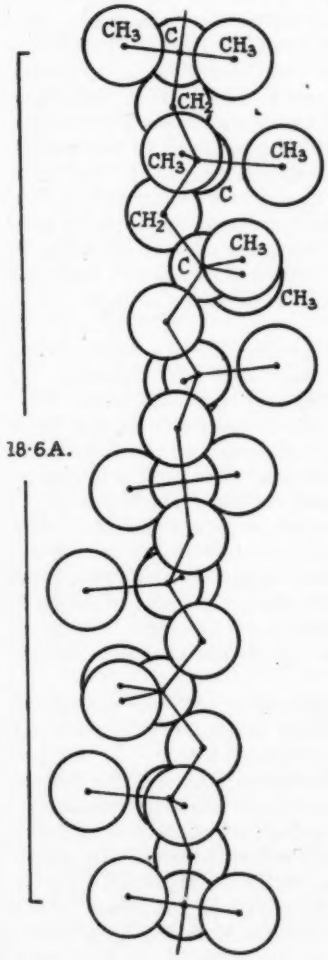
To determine the configurations of shortened chains, it is necessary to attempt a much more detailed interpretation of the *X*-ray diffraction patterns. And I think it is usually necessary to determine the complete atomic structure of the crystalline regions, by finding first of all the dimensions of the unit cell from the positions of the reflections, and then the co-ordinates of the atoms by a consideration of the relative intensities of all the reflections. It is not sufficient to consider a few outstanding reflections or a particular set of reflections: very plausible reasons for the strength or weakness of particular reflections can often be devised, which fail to account for the intensities of other reflections when these are brought into consideration. The aim should be to account for the entire diffraction pattern.

Let us look at two examples in this light: the two chemically similar polymers, polyvinylidene chloride and poly*iso*butene, which, if polymerisation is consistently head-to-tail in both cases, are $[-CCl_2-CH_2-]_n$ and $[-C(CH_3)_2-CH_2-]_n$. For polyvinylidene chloride the repeat distance is 4·7 A. (Fuller, *loc. cit.*)—very appreciably less than the length of two zigzags in a fully-extended chain (5·06 A.). For a four-atom repeat the number of ways of achieving the observed shortening is not large; and it being assumed that the polymer is head-to-tail so that the chlorines are on alternate carbon atoms, the probable origin of such shortening is to be seen in the overcrowding of the chlorine atoms. Fuller finds that if rotation round chain bonds is made to the extent necessary to ease the packing of the chlorine atoms, the rotation being in opposite directions for alternate chemical units (see Fig. 2), the correct repeat distance is achieved. This seems significant, and it is not easy in this simple case to think of other ways of obtaining the required shortening. It is not, however, certain that the substance is a head-to-tail polymer; the *X*-ray evidence, as far as it has been interpreted, does not establish this. Complete structure determination is desirable to settle the question.

For a stretched thread of the rubber-like substance poly*iso*butene, the repeat distance (Brill and Halle, *Naturwiss.*, 1938, **26**, 12; Fuller, Frosch, and Pape, *J. Amer. Chem. Soc.*, 1940, **62**, 1905) is very much longer—18·7 A.—and is also of such a magnitude that shortening of the chain is indicated: 18·7 A. is more than 7 and less than 8 times the length of one zigzag in a fully-extended chain. There are evidently at least 8 chemical units in the geometrical repeating unit; and the occurrence of strong reflections on the eighth layer line suggests a sub-period of one-eighth of the whole repeat and is thus consistent with the idea that the number of chemical units is eight and not more. The number of ways of shortening a sixteen-atom chain unit from 20·2 A. (the fully-extended length) to 18·7 A. is large; and in looking for clues to the correct configuration it is natural to consider the effects of overcrowding of the methyl groups, which is even more severe than in the case of polyvinylidene chloride because methyl

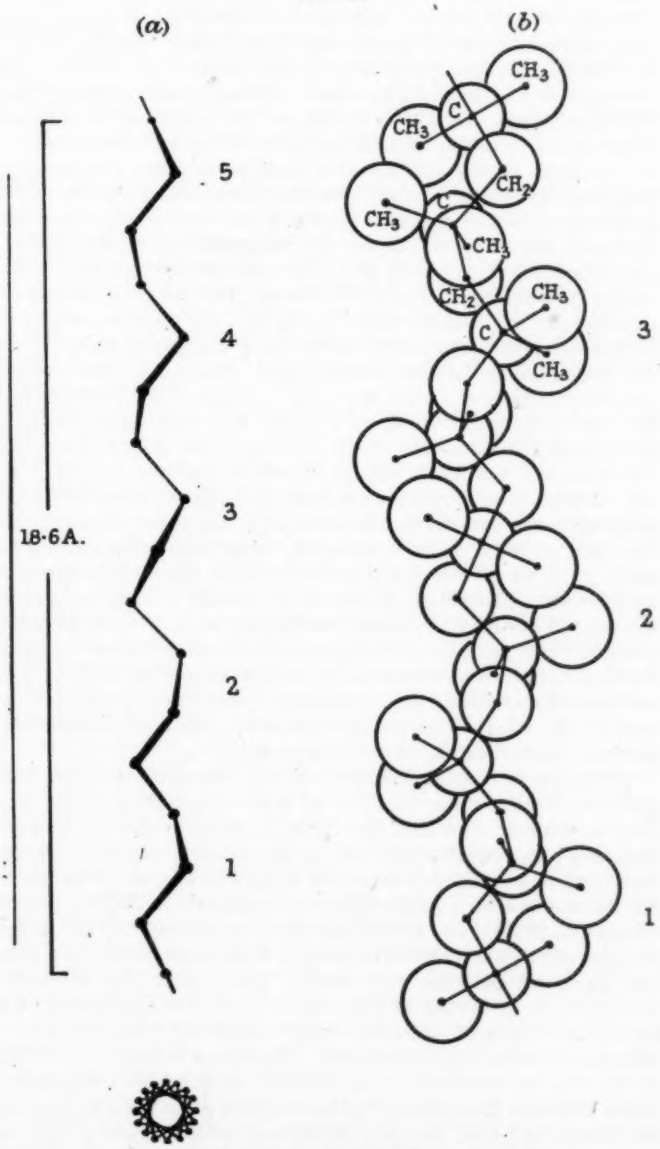
groups are larger than chlorine atoms. Fuller, Frosch, and Pape (*loc. cit.*) found that if a rotation of the same type as that suggested for polyvinylidene chloride is made, but in this case consistently in the same direction, a helix is formed (Fig. 3) which has a sixteen-atom repeat distance of 18·7 A. The correspondence with the measured repeat distance seems signi-

FIG. 3.



Helical configuration suggested for polyisobutene by Fuller, Frosch, and Pape.

FIG. 4.



Configuration now suggested for polyisobutene.
(a) *Chain alone (below—end view of chain).*
(b) *Chain with methyl groups.*

ficant; but I do not think this configuration is likely to be correct, for the following reason. The methyl side groups on such a helix stand well out from the chain, and in a side view the carbon atoms of the methyl groups form a pronounced S curve (with of course only one S in the complete period); this feature would give some strong reflections on the first layer line, yet actually all the first-layer-line reflections in the diffraction pattern of poly*iso*butene are

weak. Moreover, there are other outstanding features of the diffraction pattern which the simple helix does not account for: just as the group of strong reflections on the eighth layer line suggests a sub-period of $c/8$, so a group of strong reflections on the fifth layer line suggest a sub-period of $c/5$. The simple helix does not account for this; nor does another configuration suggested by Fuller, Frosch, and Pape, obtained by four rotations in one direction followed by four in the opposite direction. The combination of $c/8$ and $c/5$ seems in fact a very odd combination of sub-periods, difficult to account for by any straightforward scheme of shortening. Just before the war, I spent some time trying to solve the problem in detail. All the data for a detailed solution are present in the diffraction pattern, which is probably the sharpest and most perfect given by any chain polymer; and interpretation as far as the deduction of unit cell dimensions and the indexing of the reflections has been achieved by Fuller, Frosch, and Pape (I can confirm their conclusions from my own work); but the determination of atomic co-ordinates in the unit cell is a problem of great complexity, because the repeat distance is so long and there are so many possible chain configurations. After examining many possibilities, I did come across a type of helix which can account for the odd combination of sub-periods ($c/5$ and $c/8$), as well as for the intensities of many of the reflections. Although the interpretation is not complete and it is still not certain that this is the correct configuration, it is worth mentioning as by far the most promising of the many configurations which have been considered. It is illustrated in Fig. 4. To make a model, starting from the plane zigzag, it is necessary to rotate each unit much further than in Fuller, Frosch, and Pape's helix, all the units being rotated in the same direction. The chain itself then forms a helix which can be represented, using the nomenclature I have suggested (*Proc. Roy. Soc.*, 1942, *A*, **180**, 67), as a distorted form of B_{16} or the enantiomorphous C_{16} (Fuller, Frosch, and Pape's helix being a distorted form of A_{16}). In a side view the chain (Fig. 4*a*) exhibits five "crinkles", and this feature accounts for the strong reflections on the fifth layer line; the methyl groups are so disposed that there are three groups along each side of the chain (Fig. 4*b*), and this feature accounts for the great strength of one reflection on the third layer line (113 + 203); these statements have been confirmed by calculations, and in fact the intensities of most of the low-order reflections are satisfactorily accounted for. The bond angles of the chain carbon atoms must be opened a little to give the correct repeat distance; this increase of bond angles seems not improbable, in view of the gross overcrowding of the methyl groups. I hope to be able to resume this work, for the configuration of this molecule is of great interest. Poly*iso*butene is a rubber-like substance with very high extensibility and remarkably perfect crystallisation on stretching; both these properties would seem to suggest very great (not to say unique) molecular flexibility, which is remarkable for a molecule in which there is extreme overcrowding of the side groups.

This discussion has brought out the necessity of detailed interpretation of *X*-ray diffraction patterns for the determination of the configuration of those polymer molecules which are not fully extended; the aim should be to account for the entire diffraction pattern. It has also included some mention of one of the possible causes of chain-shortening, namely, the mutual repulsion of substituent atoms or groups of atoms. This factor may also be partly responsible for the non-planar configurations of molecules of the polyisoprene group, which have been determined (Bunn, *ibid.*, p. 40) by detailed interpretation of the *X*-ray diffraction patterns. In rubber and gutta-percha, which are *cis*- and *trans*-isomers of polyisoprene $[-CH_2-C(CH_3)=CH-CH_2-]_n$, the repulsion between the methyl group and the adjacent CH_2 group of the chain would be expected to favour a non-planar chain configuration. The same is true for polychloroprene, in which a chlorine atom takes the place of the methyl substituent. It is not certain, however, that this is the only factor concerned. It has been pointed out (Bunn, *ibid.*, p. 67) that in saturated molecules the most stable configurations (those found in crystals) are those in which the bonds of linked carbon atoms are staggered, the planar zigzag configuration of polythene (*idem*, *loc. cit.*, 1939) and other chains being one of the possible staggered configurations, and the meandering configuration in rubber hydrochloride (Bunn and Garner, *J.*, 1942, 654) being another; and there are suggestions (Bunn, *Proc. Roy. Soc.*, 1942, *A*, **180**, 67) that the reason why the staggered configuration is favoured is not to be found simply in the repulsions between the atoms held by the bonds, but that there is some bond-orientation effect. The "principle of staggered bonds", applied to a polymer molecule having a double bond in the chain, gives a non-planar configuration like that actually found in these substances (if account is taken only of the single bonds, or if the double bond is regarded as two distorted single bonds) (*idem*, *ibid.*). The relative importance of these two factors—the repulsion between substituents, or between substituents and chain atoms, on the one hand, and possible bond-

orientation effects on the other—in determining the chain configuration is not known. The question is of great interest, not only from the point of view of understanding the configurations of chain-polymer molecules in crystals, but also from the point of view of correlating molecular structure with physical properties. These two problems are closely bound up with each other. The melting points and the mechanical properties of chain polymers depend, at any rate partly, on the flexibilities of the molecules themselves; molecular flexibility depends on the energy associated with changes of configuration, and this energy is determined by the two factors mentioned—the forces between atoms on the one hand, and any bond-orientation effect on the other. The melting points of the polymers of the polyisoprene group have been discussed (*idem, ibid.*, p. 82) in relation to these stereochemical conceptions; and likewise, in the case of poly*iso*butene, it has been suggested (*idem, ibid.*) that its low melting point may be due to an opposition between the two factors, as a result of which the energy associated with a change of configuration is very small.

Problems of the relations between physical properties, molecular flexibilities and stereochemical factors are also presented by another interesting group of substances—the polyesters. Most of the *X*-ray diffraction information on these substances we owe to Fuller and his collaborators (*Chem. Reviews*, 1940, **26**, 143; *J. Amer. Chem. Soc.*, 1937, **59**, 344; 1939, **61**, 2575; *J. Physical Chem.*, 1939, **43**, 323). Detailed interpretations of the diffraction patterns have not yet been published, but the fibre repeat distances for many different polyesters are known, and show that varying degrees of shortening occur. In the decamethylene glycol series the chains are only slightly shortened (by about 0·2 A. per chemical unit), and therefore have an almost fully-extended plane zigzag configuration.

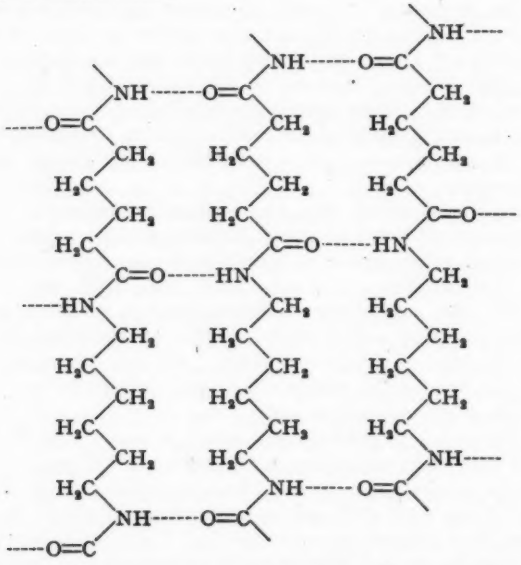
In the ethylene glycol series of polyesters there is a small, almost constant shortening of 0·3—0·4 A. per chemical unit, suggesting that in the region of the glycol group there is a uniform departure from the plane zigzag chain form. The configuration of the ester group in these substances will not be known until detailed interpretation of the *X*-ray patterns is achieved, and at present can only be a matter for speculation. Likewise, the question to what extent this departure from the planar chain form is bound up with the molecular flexibility suggested by the low melting points (Carothers and Arvin, *J. Amer. Chem. Soc.*, 1929, **51**, 2560; Fuller, Frosch, and Pape, *ibid.*, 1942, **64**, 154) of these substances is also a matter for speculation. Flexibility at the ester group is also suggested by the very interesting behaviour of some of the polyesters of the trimethylene glycol series, drawn fibres of which show a change of diffraction pattern on stretching (*idem, ibid.*); the change of diffraction pattern, since it involves a lengthening of the fibre repeat distance, indicates that the chains, which are at first considerably shortened (much more so than in the majority of polyesters), are straightened out by stretching. This behaviour recalls that of the fibrous protein, keratin (Astbury and Woods, *Phil. Trans.*, 1934, *A*, **232**, 333); these polyesters are the first synthetic polymers of comparatively simple chemical structure which exhibit this phenomenon, and it is to be hoped that detailed studies of the molecular configuration before and after stretching will be undertaken.

The manner of arrangement of polymer molecules in the crystalline regions is, from the point of view of physical properties, probably of no great significance in the case of hydrocarbon polymers or others in which there are no strongly polar groups; the type of packing probably depends chiefly on the effective shape of the molecules. It is of greater importance for molecules containing polar groups; a knowledge of the manner of arrangement may throw light on the part played by intermolecular forces in determining the physical properties. Detailed interpretation of *X*-ray diffraction patterns is necessary to obtain this knowledge. A discovery of the unit cell dimensions may give a partial knowledge of the relative positions and orientations of the molecules, but the suggestions arising from unit cell dimensions need testing by the determination of atomic positions from the relative intensities of the reflections.

In the case of the majority of the polyesters, the lateral unit cell dimensions obtained from the side spacings (the equatorial reflections on a fibre photograph) are very similar to those of polythene and therefore suggest that the molecules are packed side by side in much the same way as in polythene; and the shape of the complete unit cell suggests the relative positions of ester groups in neighbouring molecules (Fuller, *loc. cit.*, 1940); but confirmation by complete structure determination is desirable.

In the polyamides it has long been supposed that the molecules are linked side by side by hydrogen bonds, and that these are responsible, not only for the high melting points of these polymers, but also perhaps for the high tensile strength of the fibres. Mrs. Garner and I, in an investigation finished in 1941 and soon to be published, have worked out detailed interpretations of the *X*-ray diffraction patterns of two polyamides (polyhexamethylene-adipamide

and -sebacamide) and have found good evidence for the existence of hydrogen bonds. We find, not only that the oxygen atom of one molecule is on the same level as the nitrogen of the next, but also that the distance between these two atoms is that characteristic of hydrogen bonds in other crystals (2·8 A.). The hydrogen bonds do not link the molecules together three-dimensionally, but only in sheets thus :



The links between sheets (which are packed in such a way as to give triclinic symmetry) are evidently much weaker. This type of arrangement influences the orientation taken up in the cold-drawing of fibres: Fankuchen and Mark (*J. Appl. Physics*, 1944, **15**, 364) found that in the early stages of drawing, a sheet orientation occurs, and we find that it is the hydrogen-bonded sheets that become parallel to the direction of drawing; only in the later stages is the well-known chain orientation (with the chain molecules parallel to the direction of drawing) obtained. The sheet structure of the crystalline regions is also responsible for the fact that it is possible, by pressing or rolling specimens, to impose a remarkably good plane orientation in addition to the usual longitudinal (fibre) orientation; the hydrogen-bonded sheets become roughly parallel to the plane of the pressed or rolled specimen.

The detailed study of the configuration and arrangement of molecules of the comparatively simple synthetic polymers is interesting, not only in connection with the properties of these substances themselves, but also because it may throw light on the much more complex problems presented by natural polymers such as proteins. This is well illustrated by the work on nylon just mentioned, for there are some striking correspondences between the crystallography of nylon and that of β-keratin. The double orientation in pressed nylon specimens is entirely in line with that found by Astbury and Sisson (*Proc. Roy. Soc.*, 1935, *A*, **150**, 533) in β-keratin pressed in steam, and the crystal planes involved appear to correspond; the weakness or absence of reflections for certain zones in the β-keratin photograph (Astbury and Street, *Phil. Trans.*, 1931, *A*, **230**, 75) is also paralleled in nylon; and the photographs of both substances often show streaks on the layer lines, indicative of partial disorder in some of the crystalline regions.

The contributions of *X*-ray diffraction studies to our knowledge of the structure of high polymers are mostly confined to crystalline polymers. In the attempt to understand the physical properties of polymers in terms of their molecular structure, the policy of the *X*-ray worker must be to learn as much as possible about the crystalline polymers, and it may then be possible to apply the fruits of that knowledge to the non-crystalline, glass-like polymers. But it is worth remarking that even the negative evidence of non-crystallisation (of polystyrene, polymethyl methacrylate, and polyvinyl acetate, for example) is instructive. It is noteworthy that those polymers which do not crystallise or crystallise poorly, like polyvinyl chloride, are those in which there is the possibility of the occurrence of left- and right-handed groups indiscriminately along the chain; in polystyrene, for instance, the benzene ring may be attached indiscriminately to either of the two available bonds of the chain carbon atom. Molecules

which are geometrically irregular in this way would not be able to form crystalline arrangements. On the other hand, this type of irregularity cannot occur in the case of molecules bearing two identical atoms on the same chain carbon atom, and it is significant that such polymers (*e.g.*, polythene itself, polyvinylidene chloride, poly*iso*butene, the unsubstituted polyesters and polyamides) crystallise well. The point is of practical importance : anyone setting out to make new glass-like polymers would be ill-advised to use symmetrical monomers.

Discussion.

Dr. D. J. Crisp : The idea put forward by Mr. Bunn, that randomly arranged optical antipodes might account for the lack of crystallinity in certain vinyl polymers such as polyvinyl acetate, was suggested by Staudinger ("Die hochmolekularen organischen Verbindungen," Berlin, 1932, p. 114), and criticised by Meyer ("Natural and Synthetic High Polymers," New York, 1942, p. 106). The difficulty lies in the fact that polyvinyl alcohol, derived by simple hydrolysis of the acetate, presumably without intramolecular rearrangement, is crystalline. Hence structural regularity about the main valency chain does not appear to be the only factor.

Mr. C. W. Bunn : The apparent geometrical regularity of polyvinyl alcohol (the evidence for which is the crystalline *X*-ray diagram) does not prove that polyvinyl acetate is geometrically regular. If, in the hydrolysis, the acetate groups come off whole (*i.e.*, the break is between the oxygen and the chain carbon atom), then momentarily the chain carbon atom has a free bond, the hydrogen atom on this carbon atom might change over from one stereo-position to the other. In this case there is the possibility that geometrically regular polyvinyl alcohol might be produced from irregular polyvinyl acetate. Thus it is not certain that polyvinyl acetate has a regular structure.

Prof. Melville : If polyvinyl alcohol is reconverted into polyvinyl acetate, the latter is found to be again non-crystalline.

Mr. C. W. Bunn : That seems a more serious objection : from regular polyvinyl alcohol one would expect to get regular polyvinyl acetate, but even this is not certain ; a change of configuration may take place when there are free bonds on the chain carbon atoms, if the break occurs between the oxygen and the chain carbon atom. But whatever is the truth about this particular case, the statement I made is generally true—that those polymers whose molecules may be geometrically irregular through the occurrence of left- and right-handed groups indiscriminately along the chain are either non-crystalline (polystyrene, polymethyl methacrylate) or poorly crystalline (polyvinyl chloride, polyacrylonitrile), whilst those polymers in which such irregularity cannot occur (polythene, polyvinylidene chloride, poly*iso*butene) crystallise well. I do not think polyvinyl acetate has a regular structure and even if the explanation I have suggested of the polyvinyl alcohol–acetate case is not correct, then I think some other explanation will be found which is consistent with geometrical irregularity in the acetate.

Dr. Ian MacArthur : Structural discussion today has centred on the chain type of macromolecule. The characterising features of all types are the relative strength and stability of the constituent (as against the inter-) links. The nature of these, and particularly their directional bias, determine the conditions under which the metrical techniques are most serviceable. Where the polar groups are not too numerous, bulky, or reactive, and the physical state allows mobility, statistical and thermodynamic methods, as Dr. Gee has stressed, give a close approximation to experiment; entropies, not energies, are the dominant factor in long chains as such : chemical nature is subsidiary. The infra-red technique is more specific. With the speed and accuracy of the newer instruments, the present stage of collection, correlation, and semi-empirical diagnosis is still more profitable than approximate synthetic calculation.

I agree with most of Mr. Bunn's remarks, and appreciate that he deliberately restricted to crystallographic aspects. The view (Fankuchen, *Ann. Rev. Biochem.*, 1945, **14**, 210) that a complete crystallographic cell parameter determination is the sole or sometimes even the highest aim of an *X*-ray investigation in the macromolecular field, is unduly narrow. Macromolecules are usually protean systems with configuration a function of state of aggregation. In polythene, the confirmation, in the crystalline chain parts, of Müller's earlier structure for n-$C_{20}H_{40}$, is not more fundamental than the anomalies found in the determination, the composite crystalline–amorphous nature of the material, and the whereabouts of the small percentage of methyl groups; while structural progress in proteins has derived more real impetus and secured broader findings from the combined experimental fibrous protein and virus researches, synthetic model building, and co-operation with practical fibre industries, than from the purely

X-ray crystallographic approach. Precise atomic placings are excellent, but as a stage in indicating bond types, the genesis of aggregation, and the equilibria resulting from potential fields. Such features are often best investigated by selection and systematic treatment of the macromolecule, and by the co-operative use of all the relevant physicochemical methods. Among these the wave range of *X*-rays is specially serviceable to the physical chemist; but it is a tool to employ, not a subject for votaries; it gives evidence, not verdicts.

Quite apart from the fact that the full impact of *X*-rays on real matter is only now beginning to receive comprehensive notice, and that much of the information so yielded—questions of texture and secondary structure, deformation, thermal and elastic vibration systems, particle (as opposed to crystallite) size and orientation, degree of crystallinity, nature and degree of disorders—is frequently of more relevance than intracrystallite atomic arrangements, a too rigorous parameter analysis in macromolecules keeps length as a difficulty rather than as an opportunity. The advantages of small polar molecules to the *X*-ray analyst are that in packing neatly, they crystallise easily, have few parameters, and the answer is usually more or less known. The disadvantages are that bond lengths deduced are specially subject to local perturbation whose precise evaluation by quantum-mechanical calculation is in its earlier stages. When atomic parameters become too numerous for rigorous treatment, simply put in more! The asymptotic approach so made gives a more standard environment, proportionately diminishes end-group effects, and reduces many problems to two-dimensional ones, for the natural tendency of chains in aggregating to a minumum potential is to form a rod-like shape and pack in pseudo-hexagonal parallel array. Such packings are a function of molecular shape, polarity, and internal rigidity. To a first approximation they yield cells of standard cross-section and length corresponding to the unit involved. To a second approximation these dimensions do vary, and " straight " crystal analysis, on one individual only, fails to reveal them.

Long *n*-aliphatic chains form the simplest illustration. Long-chain *n*-paraffins usually build crystal cells with a standard cross-section and a length (C) given by $C/2 = k(n - 1) + p$, where n = carbon-atom content in chain, and k and p are constants. As n or temperature varies, polymorphic transitions appear, pseudo-rhombic giving place to pseudo-hexagonal or pseudo-monoclinic forms, but zigzag chain shape and packings are essentially the same. With the insertion of small polar groups rigidly attached to the chain axis (*e.g.*, in *n*-ketones) polymorphism disappears, the addition of dipole layer to van der Waals chain forces having a stabilising effect, especially with respect to temperature variation. The position of the C=O substituent along the chain causes systematic variation. The degree of stability increases with the dipole moment of the group inserted. In all cases, temperature increase causes a nearer approach to a radial symmetry which may (certain paraffins and alcohols) or may not (acids) be reached before melting. The phenomenon argues an increased rotational or torsional vibration about the chain axis, probably of a co-operative type. The nature of this is helpfully investigated through thermal energies (Garner), intensity analysis along the chain (MacArthur), or by temperature–polarisation studies on *cis*- or *trans*-diketones (Müller). Transitional energies can be subdivided into chain and end-group elements. In general, strain in bond lengths and angles may be indicated by abnormal heats of combustion (poly*iso*butylene; Polanyi), or its absence reduces isomeric possibilities for test (benzene hexachlorides). Localised molecular weighting is valuable. Swelling or isotopic replacements may indicate particular (*e.g.*, hydrogen-bond) links. Force field theory is useful in simple cases. Although the plate (graphite, clays) and skeleton (protein) types are a natural extension from chains, they lie outside present discussion; but, particularly here, the new technique of the electron microscope with its resolving power of 25 A. has, in conjunction with *X*-rays, been of valuable and potentially enormous service.

It may well be, therefore, that the fundamental structural developments in macromolecules will be achieved, not through routine precision crystal analysis, but, as instanced in the pioneer long-chain work of the Royal Institution and the Bristol school, and in the fibre methods at Leeds, in co-ordination with ancillary techniques. Scientifically, this demands an extensive physicochemical background; technically, greater concentration on *X*-ray power, sensitivity and speed of recording, and flexibility in conditioning specimens while undergoing *X*-radiation.

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